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The University of Toronto Medical Journal

VOL. I APRIL, 1924 NO. 5

EDITORIAL

THE board of editors in this final issue, look back with considerable satisfaction over the first year of the venture of an undergraduate medical journal. The support accorded to the monthly by the staff of the faculty of Medicine, by the undergraduates, and the keen interest shown by individuals outside the University of Toronto has amply justified the attempt to publish such a periodical. Furthermore, it justifies the decision of the Medical Society to continue doing so again next year and, we hope, for years to come. For the good-will and generous backing we have received, we extend our heartiest thanks to all. Particularly do we thank the graduating year in Medicine for their generous action in voting to us the balance of the Year's funds. This sum, and a goodly sum it is, puts the JOURNAL on a sound financial footing and will enable future editors to proceed with the development of the magazine with greater confidence. We are beginning to stir undergraduate interest in writing articles and preparing reviews on subjects of universal appeal. We are looking forward to the time when the bulk of the material published will be contributed by the undergraduates of this, and we hope from time to time, of sister universities. A student who spends sufficient time reading and collecting the literature on a given subject can prepare just as valuable a paper for his fellow-student as a busy member of the staff. The value to the student preparing the paper is inestimable. It gives him an insight into and an understanding of the particular topic that is always a source of great benefit and satisfaction. We would suggest that students who are so situated this summer that they can devote some time to the job, should come back in the fall with an article for the JOURNAL. The editors hope that this suggestion will meet with responses from more than one undergraduate who appreciates the value of "getting up a paper".

DR. THOMAS McCRAE of Philadelphia, in the notable address which he delivered at the annual dinner of the graduation class in medicine here last month, had some significant things to say concerning the reading which medical students and those commencing the practice of the profession should strive to do. To undergraduates he would suggest three sources to begin with—Conan Doyle's "Sherlock Holmes" series to learn the art of observation, Kipling's "Kim" to learn the value of observation and keeping one's counsels, and George Eliot's great novel "Middlemarch" to study the character of the physician. Assuredly Dr. McCrae believes in starting with the lesser voices of litera-

ture and is content in the hope that a reading of the great classics will follow. We would recommend such a course to the readers of this journal. Read the above books for what they will teach you in the art of the profession of medicine; then extend your field and read not for this mechanical value but for the spiritual value of the books.

Of "Middlemarch" which Dr. McCrae mentions, Stephen Paget has this to say: "Read 'Middlemarch' I say to all students. Lydgate (the doctor in the story) died long ago; when he started into practice, most medical practice was still strutting or shambling along the old paths. But the whole story of his life will help you more than all the novels of the last quarter century—if Lydgate's life does not touch you ask yourselves whether you have any call to be doctors."

Those who listened to Dr. McCrae were inevitably reminded of the great Osler with whom he worked for years—Osler who always spoke in the robes of the great tradition. To the student who seeks guidance in his reading of the great authors Osler makes repeated suggestions. He would put at the top of the list the Bible, Shakespeare, Sir Thomas Browne's Religio Medici, Epictetus and Marcus Aurelius, Jowett's translation of Plato, Montaigne's Essays, and the "Breakfast Table Series" of Dr. Oliver Wendell Holmes. You as the student, Osler says, "will need strong leaven to raise you above the dough in which it will be your lot to labour", and these books supply the imaginative force which may be lacking in the busy daily round. If one would turn from the greater classics, for we are not always "tuned to the tang of Stevenson or the burr of Dr. John Brown", one would be tempted to add to the above list the Essays of Osler himself, Stephen Paget's "Confessio Medici", "The Corner of Harley Street", and any of the writings of Sir Clifford Allbutt (if one would acquire a style).

The modern world is questioning all the old orthodoxies; it cannot dispute the value of literature, the record of the chosen few. The medical student who would touch the world at many points would do well to temper his science with what within medical walls is so frequently termed "outside reading".

NERVE cells because of their long processes extending into the peripheral nerve, are so different from other cells that many observers have regarded them as being many-celled in their development. Whether the peripheral nerves are outgrowths of neuroblasts or are formed by sheath cells in situ, has been a subject of great controversy. In our neurological studies as medical students we are being taught dogmatically that the peripheral nerves are developed as outgrowths of the cells in the posterior root ganglion and the anterior column of gray matter. This teaching is part of the now accepted neuron theory the first proposition of which as stated by Ranson is "The neuron is the genetic unit of the nervous system—each being derived from a single embryonic cell, the neuroblast".

Prof. Harrison of Yale University gave experimental backing for the theory when in 1906 he showed that a neuroblast grown in clotted lymph did develop a long axon in the course of a few hours. Prof. Harrison by some further observations and experiments, the results of which are soon to be published, still further substantiates the theory. He has shown that all the sheath cells, neurilemma cells, are derived

from the neural, or ganglionic crest and grow out along the nerve fibres to cover them.

He removed a thin strip, including the ganglionic crest, from the backs of frog embryos with the result that the sensory nerves did not develop at all and the motor nerves appeared as sheathless axones. When he removed the ventral half of the cord sensory nerves developed but motor nerves did not. When he removed the medullary cord after the spinal ganglia were formed only sensory nerves developed.

Further, he observed in the fin fold of living tadpoles the actual movement of sheath cells along the already developed sensory fibres. The rate of movement of these cells may exceed 1μ per minute. In the urodele fin he observed that a plexus of naked nerve fibres developed first, sheath cells later covering them.

Prof. Harrison concludes from his experiments and observations that "the ganglion cells are the essential elements in the histogenesis of nerve fibres. The sheath cells are to be regarded as a peripheral neuroglia."

It gives a feeling of security to those of us who have succeeded in mastering the neuron theory and to those who have come to interpret nervous diseases with it as an anatomical basis to know that it is being thus substantiated and is likely to pass over from the realm of theory to that of fact.

OWING to the constancy with which haemolytic streptococci of one kind or another have been found associated with scarlet fever, they have long been considered as a possible cause of the disease. Attempts to prove their causal relation have encountered many obstacles, chief of which has been the failure to produce experimental scarlet fever. The occurrence of haemolytic streptococci in connexion with scarlet fever has been noted in the epidemic of the mild form of the disease that occurred in Toronto this winter. This observation serves to enhance for us an interest, already keen, in the exhaustive researches that are being prosecuted in different parts of the world toward the discovery of the causative organism of this wide-spread and important condition. Particularly interesting are the investigations of Drs. George and Gladys Dick of Chicago, whose work has been reported in the *J.A.M.A.* They claim that the responsibility lies at the door of a particular strain of haemolytic streptococcus which they have isolated. They state that it fulfills all of Koch's laws and is the organism of scarlet fever. Furthermore, they have devised a skin test for susceptibility to scarlet fever reported in the same journal. The *British Medical Journal* comments editorially on the work of these investigators in a March issue. Certain workers have claimed that the organism causing the disease is a minute anaerobic diplococcus. Their findings have not been upheld, but on the other hand many investigators have for some time regarded certain strains of haemolytic streptococcus with suspicion and it looks as though Dr. Dick and his sister were proceeding rapidly in the right direction. Independent investigations in other quarters are required before the problem can be regarded as solved, but in the meantime their work in Chicago will be followed with close interest in view of the striking evidence they have adduced on behalf of their streptococcus.

THE UNIVERSITY OF TORONTO

THE undergraduate at large who is still in the midst of obtaining a grasp of the better understood medical and surgical conditions in the preparation for his degree, will be interested to know that in the tremendous amount of research work going on in all parts of the world along various lines, the old enemy and bugbear of the physician, the common cold, is not being neglected. In a recent issue of the *Journal of Experimental Medicine*, Olitsky and McCartney publish the result of an investigation of the nasopharyngeal secretions from patients with common colds. They transmitted the condition from subject to subject, using filtered nasopharyngeal washings from carefully selected cases. The secretion in all cases had to be derived from patients in the early hours of the disease. Transmission was not affected when washings were used from patients who had had the condition for 18 hours or more. Their work indicates that the incitant of common colds is filterable, thus confirming earlier findings in this connexion. In aerobic cultures they failed to find any predominant pathogenic organism. In no case was Bacterium pneumosintes seen, and the globoid bodies of Foster were not isolated. Anaerobically they cultured several organisms of an anaerobic, Gram-negative, filter-passing character, previously described by Olitsky and Gates, but the field is still fertile for investigation.

BACK numbers of the JOURNAL (with the exception of the December number) can be obtained at the usual rates by applying at the office of the Medical Society, room 107, Anatomy Building.

MEDICINE IN THE OLD TIMES

A writer in a current English journal who has recently been studying the early English newspapers, sets down some of the results of his researches which make most interesting reading. The advertisements at that time were known as "advices" and were taken advantage of by the medical profession of the day. In the columns of the London *"Public Adviser"* in the summer of 1657, there appeared the following delightful announcement:

"A Doctor of Physick, lately come from beyond sea, whose education, private study and foreign travel, hath given him advantages above others, cures by God's assistance all manner of Diseases curable by art, with as much speed, perfection and facility as is possible, as the inveterate Pox, the Palsie, Madness, Mopishness, Swooning, panting and trembling of the Heart, the Megrim, Sore Eyes, King's Evil, Jaundies, Scurvie, Green Sickness, Agues, Coughs, Consumptions, Dropsies, the Collick, and many others. He lieth in St. Martin's Lane in the Fields at the sign of the Sugar-Loaf, at a Grocer's house in Newstreetend."

London's streets were once a very forest of signs. Those were the days before the houses were numbered. The sign system must have been extremely cumbrous, as we may judge from the advertisement of Dr. James Tilborgh, a medical man, who in the eighteenth century advertised that he "liveth at present over against the New Exchange in Bedford Street, Strand, at the sign of the 'Peacock', where you shall see at night two candles burning within one of the chambers before the balcony, when he may be spoke with, alone, from eight in the morning till ten at night."

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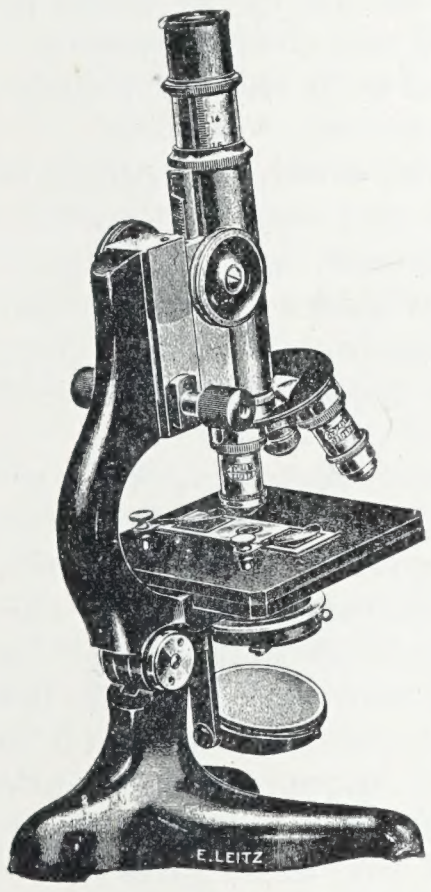

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TUMOURS OF THE BREAST

By A. Primrose

Professor of Clinical Surgery and Dean of the Faculty of Medicine, University of Toronto

If a patient consults you because of a lump in the breast an accurate diagnosis of the nature of the tumour is of paramount importance. It is essential to recognize malignancy early if we are to save life by a radical operation. Many suggestions have been made in the attempt to wrestle more effectively with the problem of the cure of cancer of the breast. It is a treacherous and terribly fatal disease.

These suggestions have included attempts by improved technique to perform a more radical operation, and the more skilful use of radium and X-ray therapy. In spite of all efforts we are compelled to admit that we have no certain means of eradicating breast cancer once there is a primary growth with secondary metastases in the adjoining lymph-nodes. To-day the greatest safeguard to the public is the early recognition and the early and thorough removal of the cancer growth. No remedial measures can compete in effectiveness with the early diagnosis and immediate removal of the disease by operation.

Recently the writer published a paper in which he presented a study of 448 cases of breast tumour—of these 291 were malignant and 157 benign. In malignant cases the oldest patient operated upon was 80 and the youngest 28 years of age. In benign cases the oldest patient was 61 and the youngest 19 years of age. Malignancy was most common between 40 and 50 years of age (36.4%) and simple tumours between 30 and 40 years of age (42.3%).

Tumours of the breast may be inflammatory in origin, or they may be new growths. Mastitis is exceedingly common, both acute and chronic, with or without suppuration. Tuberculosis, syphilis and actinomycosis constitute the rarer forms of specific breast infection resulting in tumour formation. By far the most common malignant growth in the breast is cancer, while sarcoma occurs as a very rare event. Of benign growths we have adenomata or fibro-adenomata and much more rarely such tumours as angioma, myxoma and lipoma. The tendency to cyst formation in tumours of the breast is very marked, and is found both in inflammatory conditions and in new growth. The relationship of cysts and papillomata in the breast to the subsequent development of new growths has been recently studied by Sir George Cheatle. He has shown the connection between cystic and epithelial changes, on the one hand, and the development of new growth of a simple or malignant type on the other. The technique which Cheatle employed was to make whole sections of the entire breast with a very large microtome and to study the relationship of cyst formation to the gland ducts and the gland acini along with the epithelial hyperplasia accompanying the cyst formation. He showed very conclusively that the cystic state acted as a predisposing and determining cause in the initiation and growth of tumours both simple and malignant.

Bloodgood has recently advocated conservative (non-operative)

measures in the treatment of benign lesions of the female breast. Unfortunately errors in diagnosis, even in the most competent hands, are not uncommon: the difficulty is to make sure that we can exclude malignancy at the time of our examination or to be certain that the tumour which we refuse to operate upon will not subsequently become malignant (*vide* Cheatle's observation quoted above). I have reported in a recent paper, the details of certain cases which seemed to fulfil Bloodgood's claims for a diagnosis of benign tumour but which subsequently, at operation, proved to be malignant. We must therefore protest against the teaching of Bloodgood and favour rather that implied in the aphorism of his colleague Doctor Finney when he said "Any lump in any woman's breast is better out than in".

In studying the clinical manifestations of a tumour of the breast one finds the diagnosis of malignancy easy when the condition is advanced. Unfortunately by the time such an advanced stage is reached it is too late to save the life of the patient. Hence it is necessary to study with extreme care the early signs of mammary cancer. Let me give a typical example: A patient 65 years of age, at present under my care in the hospital, noticed a lump in the left breast six months ago. It was painless and did not seem to increase in size. On examination I found a tumour the size of a small walnut, in the lower and inner quadrant of the breast, hard as a rock, possessing a somewhat irregular surface, freely movable on the deeper parts. On examining the relation to the skin with meticulous care one found a slight but definite pull upon the skin when moving it over the tumour. This pull would be easily overlooked if the examination were not made with great care. A lymph gland was palpable in the axilla. This again was only found after careful search. A radical operation was performed. The tumour showed the histological picture of carcinoma with strands and cords of atypical epithelial cells possessing many mitotic figures. The lymph glands showed hyperplasia of endothelial amd lymphocytic elements but no secondary cancer.

The prognosis in such a case is excellent: one may comment that the patient ran great risk in leaving it so long (6 months) after it was first discovered. Fortunately it was, for a time at least, very slow in growth and development but it might well have been otherwise. The favourable outcome in this case is not an argument against early operation. One cannot tell the nature of an individual tumour by gross examination: it may or may not be of that rapidly growing, medullary type, which brooks no delay. Let me therefore once more insist upon the *immediate* investigation of a lump appearing in any woman's breast. The condition of the axillary lymph glands in this case is also interesting: it presents no evidence of secondary growth but the hyperplasia depicts a condition which Ewing has described as "precancerous condition of the lymph nodes".

Let me protest against the routine employment of the so-called "quick section" at the time of operation. It has been considered by some an ideal method of securing a certain diagnosis. My objections are, in the first place it may disseminate the cancer in our manipulation to secure a piece of the tumour for section and in the second place it is by no means always reliable. In a woman of forty-nine a radical operation was performed on a clinical diagnosis of breast cancer. The

pathologist reported chronic mastitis without malignancy. Through an accidental circumstance the axillary glands were lost sight of and were not examined for some days subsequently; undoubted cancer was eventually found in the glands· the breast was again carefully searched, and now a small focus of malignancy was discovered, surrounded by a large area of chronic inflammatory change. Among other things this illustrates the futility of trusting to a quick section in such a case.

The quick section however has its place, namely in those cases where we consider we can reasonably exclude the presence of malignancy in our clinical examination. Here we proceed to perform a conservative operation and in such cases the pathologist is present to make a quick section lest the diagnosis be wrong. If malignancy is discovered one then proceeds to complete the radical operation. Where however one can make a reasonable diagnosis of cancer, the radical operation should be undertaken without the preliminary quick section.

The implantation and dissemination of cancer during our operative procedures is a danger which must be guarded against in our operative technique. This danger exists in our operations for breast cancer. It is a very real danger in the manipulation of the cancerous breast prior to the operation or in the method of scrubbing and preparing the parts to secure an aseptic field. The nurse who is undertaking the preparation should have explicit instructions in this regard. The writer has long held these views and has insisted upon the greatest gentleness in manipulating a cancerous breast both before and during operation. Dr. Leila Charlton Knox has recently published a paper on "The Relationship of Massage to Metastasis in Malignant Tumours". She carried out numerous experiments in mice; for example, in one series the animals were inoculated subcutaneously in the inguinal or axillary region with mouse carcinoma; the resulting tumour, when it reached the size of 5 mm. in diameter, was vigorously massaged for one minute on two consecutive days; the tumours were then excised and the animals killed twenty-seven days later. In a large percentage of the cases metastases were found in the lungs. In another series of experiments very gentle massage was carried out every day for a fortnight with similar findings. Experiments of this nature are instructive and suggestive, the results obtained are quite in harmony with our knowledge of the dissemination of cancer in man.

One cannot in this paper describe in detail the radical operation for breast cancer. The principle involved is that common to all operations for cancer, namely thorough removal of the primary growth along with the glands, and gland bearing fascia, of the regions toward which the lymph from the affected part is drained. The breast is developed in the superficial fascia, hence its close relation to the skin: normal breast tissue has also been demonstrated invading the deep fascia over the pectoralis major muscle. The operation therefore includes removal of the breast with the skin over the tumour, the costo-sternal part of the pectoralis major muscle, the pectoralis minor muscle and the glands and fascia of the axilla. The pectoralis minor muscle must be removed else it is impossible to dissect out the glands and fascia behind that muscle and the costo-coracoid membrane. The dissection of the axilla must be continued right up to the clavicle. All these tissues, the breast, the pectoral muscles, the glands and fascia, must be removed in one

mass, so that cancerous areas are not cut across and the disease by such means disseminated.

The end results were carefully studied in a series of 76 consecutive cases of cancer of the breast. One found that the percentage of "cures" (*i.e.*, patients who had lived 5 years and over without recurrence) was 44.4%. This is perhaps a little better than the average percentage obtained and published by other surgeons. The most interesting study of my results however is embodied in the following table

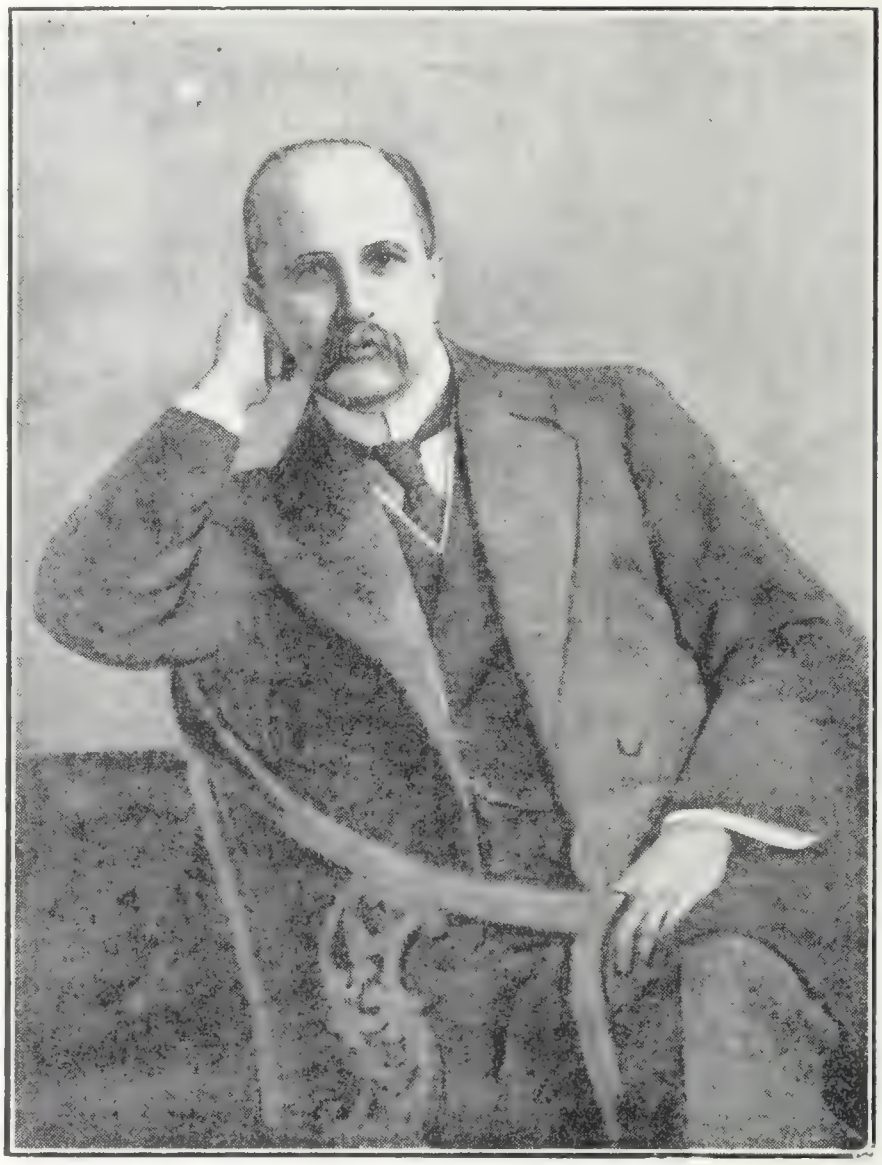
CLASSIFICATION OF END-RESULTS IN FORTY-FIVE RADICAL OPERATIONS

	Cases	Cures	Percentate of cures
1. Early favourable (no glands involved)	11	10	91%
2. Favourable (glands slightly involved)	13	8	61%
3. Average cases (glands markedly involved)	21	2	9%

These figures prove that cancer of the breast can be eradicated and permanent cure effected provided the operation is undertaken early. This lesson is the one, above all others, I am anxious to emphasize in this paper.

I regret the limits of the paper will not permit me to discuss distant metastases in cancer of the breast. Bone metastases are quite common. In my series I have found them in many of the long bones, the spine and in the cranial diploe. Not infrequently they are multiple, in one of my patients they occurred in the femur, the ribs, the humerus as well as in the cranial diploe. Such manifestations are so common that when a patient, particularly at the cancer age, complains of pain in bone of doubtful origin it is always well to examine for any primary focus of cancer especially in the breast. It is often easy to overlook this etiological factor in referred pain. One of my patients with a secondary deposit in the spine had her appendix removed because the surgeon interpreted her referred abdominal pain to the appendix!

In the beginning of my paper I stated that by far the most important factor in determining the efficacy of our treatment in mammary carcinoma is the duration of the disease prior to operation. One can assert that the greatest advance in the past decade, in securing improved results and in saving life, lies in the fact that patients come earlier to the surgeon for treatment. That patients do come earlier is shown in my statistics extending over twenty years. Taking those who come to operation one month and under one month from the time the initial symptoms appeared, I find that in the first decade only 8.4% came thus early, while in the last decade no less than 27% came at this very early stage when there was an excellent prospect of complete cure.



SIR WILLIAM OSLER

SIR WILLIAM OSLER: A MASTER OF MEDICINE

"The daily advent of the chief was the great event. An example of punctuality, he was ever before the hour bringing the freshness of the morning with him. On his breezy entry, with quick, springing step and gay manner, our world brightened. A distinguished gentleman, he radiated a dignity by his very evasion of it. On his way to the wards linking some companion affectionately by the arm, he cheered every one he met by his friendly word, nod, or wave of hand.

At the bedside with his group of staff and students, he made a striking picture. All faces were expectant. The patient was at once put at ease by some sympathetic enquiry, often with a humorous turn. Osler's thorough methods of investigation and teaching need no description here. His arrangement of facts usually made the diagnosis self-evident. Then came the easy intimate talk upon the case in simple, exquisite English. There was no suggestion of *tour de force*, nor of climax, yet every word was pointed and every sentence worth remembering, often driven home by a delightful humour. Just at first the low, modulated voice was slightly hesitating and tremulous, revealing a little human nervousness even before that worshipping group. Medicine as revealed by him, was seen to be the pinnacle of a broad, underlying structure of science and culture, to which all sources of information contributed something of value. His talks were filled with narrations of incident of personal or historical interest and with frequent references to old teachers, to the fathers of medicine of all periods, to obscure or long-forgotten men, lifting them again to momentary fame, and to contemporaries of all countries. The English classics were often quoted and the glory of the past was so illuminated that some knowlegde of it became a necessity. Consequently the 'Golden Sayings' the 'Meditations' and the 'Religio Medici' were as readily found in the hospital bookstore as the newest text-books. His lamp shone with equal brilliance in the ward, theatre, or dispensary clinic, post-mortem room and library. Withal he was most modest."—From "Osler as an Incentive" by Dr. C. D. Parfitt.

ON SOME CONSIDERATIONS BEARING UPON THE SUCCESSFUL PRACTICE OF MEDICINE

A. G. McPhedran
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IT may be well first of all to indicate what is meant by the successful practice of medicine; it does not mean the accumulation of wealth, though occasionally that may occur; nor does it necessarily include the acquirement of a wide reputation; for wealth and reputation are sometimes achieved by the veriest quacks and charlatans, occasionally found in the profession, and found rather frequently outside of it, usually associated with some healing fad extensively advertised. But the successful practice of medicine does mean the thorough understanding of each individual condition complained of, with the application of appropriate remedies in such a way as to restore the greatest possible degree of health.

An attentive reading of the medical curriculum of any good college might well give the impression that a student after pursuing the course to the end should be thoroughly equipped for the practice of medicine. That this impression is not current among recent graduates is evident from the very general desire they have to secure interneships in hospitals, or otherwise to spend a year or more in further study. And even then probably many feel on beginning practice that their equipment is not complete, realizing that competence to treat disease successfully can come in a full degree only when they have added wisdom to their learning.

Now among factors outside of academic training necessary to practice medicine successfully one may first of all name ordinary common sense. This may be defined as that quality of mind which enables its possessor to distinguish between things that differ, to attach proper values to, and appreciate the relationships existing between, the things which he observes, and to draw correct conclusions therefrom. Dr. Oliver Wendell Holmes considered it of prime importance. "Science", said he, "is a first class piece of furniture for a man's upper chamber if he has the common sense on the ground floor; but if a man has not got plenty of good common sense, the more science he has, the worse for his patient". The University, of course, must assume that every person applying for admission as a student has been naturally endowed with that boon. And one may remark further that the acquirement of wisdom and good judgment is an impossibility to anyone not so endowed.

Because of the tremendous progress that medical science has made in recent decades it has become impossible for one mind to obtain possession of all the available knowledge of disease; it requires years of close study for one to become reasonably acquainted with that which is to be known about every medical subject; and the enormous amount of systematized facts that has to be mastered during a course of study leaves no time for the definite study of other sciences, which though they be less thoroughly developed, nevertheless sometimes have a very important bearing on the understanding of disease.

Psychology, for example, as it is known to-day, is a practically new

science. Most practitioners of medicine would disclaim any acquaintance with the subject, not because they are wholly ignorant regarding mental processes in their patients, or the changes in those processes produced by the passage of time, but because the observations they have made and the information they have gained have never become arranged in their mind in any systematic way; they know many isolated facts but are usually unprepared to make generalizations from them. And they have never read books on psychology. And yet, whether in a truly scientific way or after a stumbling fashion, we are all compelled every day of our lives to make use of our knowledge of the human mind and of its reactions to various influences brought to bear on it. The following story is instructive.

Not long ago a surgeon reported the case of a young woman who complained of considerable pain in the right iliac fossa. The associated signs and symptoms made an almost complete picture of a mild but definite appendicitis. A colleague was asked to see the patient and he also was all but satisfied that there was inflammation of sufficient severity to require removal of the appendix, but it was decided to delay, and seek another explanation of the condition. Eventually the story came out that because of domestic unhappiness, the patient's father had made her promise that she would never marry. After the promise was made all was well for a time, but it gradually became evident to the young woman that she must withdraw herself from the society of her friends for fear some man might fall in love with her and make it difficult for her to keep her promise. The mental strain of her unnatural position became so great that she fell ill and the illness took a form in which symptoms of appendicitis seemed at first sight to dominate the picture.

Having learned her story the surgeon assured her that the promise was altogether improper and she should not hesitate to break it if she wished to do so. Having become satisfied that the promise should be not only disregarded but forgotten, she was very soon restored to her usual good health.

This surgeon treated this patient as a *person*, suffering to be sure; but her suffering did not blind his eyes to her personality. In this instance at least, the emotional condition far surpassed in importance the physical discomfort. He treated her with truly Christian science. How different the results if he had treated her as a *case* and forgotten about herself. Then, undoubtedly he would have removed her appendix and received a much larger fee for his spectacular but incompetent services, but he would not have removed her discomfort nor its cause, nor started her on the road to good health. On the contrary, she would likely have become a confirmed invalid, requiring successive operations for "adhesions", and placed permanently beyond all likelihood of ever being invited to break her foolish promise.

It is quite impossible for services of this kind ever to be suitably remunerated by material things. The benefits conferred are incommensurate with any possible fee. And yet the services rendered were by no means unique either in that surgeon's experience or in the experience of the profession generally. No practitioner with his wits about him can be in practice long without having the opportunity of rendering services of this sort, and if he is worthy of the traditions of the profession he will not fail to see and use the opportunity.

Worry and anxiety from every cause or no cause, and domestic unhappiness, are prolific sources of aches and pains that have no real organic basis; and their victims may be found in every doctor's practice and in every hospital ward. It takes bravery as well as wisdom for one to undertake successful interference in home conditions; usually it is better not to attempt it but to be content merely to relieve present distress, because unsuccessful interference in such cases not only fails of its purpose but actually increases the suffering of the victim. But mental unrest from other causes than unhappy domestic relationships may sometimes be successfully dealt with, not by any pooh-pooh method, but by appeal to the patients' reason, or imagination, or former experience, or love of her children, or faith in God. Realizing that our patients are not mere physical structures operating automatically, but are of a race whose nature is excessively complex, the physical being only one of its elements, we shall not always try to quiet their complaints with a dose of Epsom Salts or an aspirin tablet.

One reason why the general practitioner has a decided advantage over the specialist in his study of a patient's complaint is just this that he has more or less intimate acquaintance with the patient himself. The day of the general practitioner is not likely to pass, because there are very many people and always will be very many people who believe in the family doctor. With the greatest reluctance they will change from one doctor to another, and when the services of specialists are required it is on recommendation of the one who knows the illness and the troubles through which they have passed in recent years. The intimate knowledge and mutual confidence which years of faithful service have established, not only assist the family doctor in understanding a new complaint, but give him also a splendid advantage in endeavoring to restore health. The "best families" recognize this and they invariably get better service than those who run from one physician to another.

Indeed the truth is that other influences than those of purely physical nature enter so generally into the production and maintenance and modification of the manifestations of disease that one should beware of ignoring or minimizing them. In reference to this, Sir William Osler thirty years ago said, "Science has done much, and will do more, to alleviate the unhappy condition in which so many millions of our fellow-creatures live, and in no way more than in mitigating some of the horrors of disease; but we are too apt to forget that apart from and beyond her domain lie those irresistible forces which alone sway the hearts of men. With reason science never parts company, but with feeling, emotion, passion, what has she to do? They are not of her; they owe her no allegiance. She may study, analyze and define, she can never control them, and by no possibility can their ways be justified to her." And he quotes from Marion Crawford ("A student of the heart of man and a depictor of his emotions"). "Look where you will throughout the length and breadth of all that was the world, 5,000 or 500 years ago; everywhere passion has swept through before it, belief and reason. Passion rules the world, and rules alone. And passion is neither of the head nor of the hand, but of the heart. Love, hate, ambition, anger, avarice, either make a slave of intelligence to serve their impulses, or break down its impotent opposition with the unanswerable argument of brute force, and tear it to pieces with iron hands".

If this be so, why is so little attention given in the curriculum to the mental, moral, and spiritual factors of disease? And again, why is so little medical literature concerned with the elucidation of these subjects? And again, why are the members of our profession, which is actually and admittedly a learned class of public servants, almost without exception intolerant of the assistance in the understanding and treatment of disease which may at least occasionally be rendered by those outside, whose training has either been quite neglected or has been along quite different lines from our own? Surely this intolerance is one of the reasons (though by no means the most important) that in these days healing cults and fads rise and flourish like mushrooms. How fortunate if they would also perish like mushrooms! But in part at least they are a protest against the poverty of our imagination which prevents us from realizing that our patients are human beings and not merely cases of pneumonia or measles.

Perhaps the answer to these questions is not difficult though the discovery of a remedy be quite otherwise or perhaps almost impossible. Without in any way disparaging attainments in the science or accomplishments in the practice of medicine by those of every age whose names are imperishably inscribed in history, one must still confess that the sum total of scientific knowledge embraces no more than the borders of vast but fertile wildernesses. Exploration is proceeding, and the inexhaustible energy and enthusiasm of the investigators is obtaining marvellous results; but surely "the best is yet to be". But, progress in the acquirement of facts and the correlation of them into science has proceeded more rapidly in the world of material things than it has in other regions, one reason for this perhaps being that material things more readily yield their secrets. Science has advanced along the lines of least resistance and the acquirement of knowledge of material things has undoubtedly been accelerated by our desire to make them contribute to our physical comfort and pleasure.

The world is so much with us, and physical (and therefore medical) science has made such great progress in recent times, that the wonder would be if we were able to resist the clamorous influence of physical forces that engage our attention so much and were able to maintain a judicial attitude between them and those other forces, wholly impalpable and invisible, unsuspected indeed by the careless and superficial, but potent in determining the forms and manifestations of disease and its reactions to therapeutic measures. Perhaps some day science *will* have opened up these other territories of human personality so that we may deal as surely with their exact relationships to disease as we now deal with germs of small-pox or malaria. In that time no doubt the course leading to the M.B. degree will differ considerably from that now followed. But meanwhile we may use such fragmentary knowledge as we have acquired, and in so doing we shall but follow precedent; for the practice of the art of medicine has always taken account of many things not included in its science.

And although, indeed, these considerations outside strictly physical science are of importance in the practice of medicine, no student really waits till after graduation to commence preparation to deal with them. Whether he will or not, his relationships with his teachers, with other students, with the sick, in class-room, in residence or boarding house,

on the campus or in the gymnasium, in the wards of the hospitals, are of necessity fitting him to deal with these considerations unless he be incapable of receiving such development and be therefore unable to make good use of his opportunities as a student. One does not like to think it possible that anyone could study the course to a degree, and become nothing more than a poor encyclopaedia of medicine. He ought to have that knowledge, but he ought to have much more; his whole personality ought to be cultivated and enriched in every particular so that he may be prepared to become a real benefactor to his community.

In the writings of Robert Louis Stevenson there occurs a generous tribute to our profession that may act as a good stimulus to high endeavor. It takes a great deal of perseverance to live up to it, but it is surely worth the attempt if only to deserve the commendation of such a man. "The physician is the flower of our civilization: and when that stage of man is done with, and only to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race. Generosity he has such as is possible to those who practice an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarrassments; and, what are more important, Herculean cheerfulness and courage so that he brings air and cheer into the sick room, and often enough, though not so often as he wishes, brings healing."

EXERCISE IN HEART DISEASE

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IT is only during the past few years that children with cardiac disease have been thought to have much chance of developing into adults capable of carrying on the ordinary routine of life. This change in view has come from the better handling of this type of case. It has shown itself particularly by our attitude towards—I, the removal of foci of infection; II, the amount of work a damaged heart can do.

In regard to the first, the removal of foci of infection as promptly and effectively as possible is most important. It should be noted that operations for the removal of foci (usually tonsils) are done much earlier than formerly, close observation having shown that the heart may suffer more from the presence of the infection than it does from any disturbance caused by the removal of the tonsils.

It is about the second point, however, that we wish to speak—that is, the effect on the heart of gradually increasing exercises. The modern advance in heart disease is somewhat comparable to that of kidney disease, in as much as the heart is now judged by the efficiency of its response to work, just as in kidney disease one endeavours to learn by the efficiency of their action, how badly diseased they are. We have

become accustomed in the past to trying to make a diagnosis of the pathological disease present, thus obscuring our view as to just how good the heart really is, measured in terms of what it can do. Not only this, but very often one is afraid to let the heart work out its own salvation by exercising its muscles properly. Besides making a pathological diagnosis therefore, it gives one much more detail on the case, if the heart be classified by its response to a set of definite exercise tolerance tests.

Before explaining the classification used at the Hospital for Sick Children a brief review of some physiological facts bearing on the action of the heart may be cited. Probably the most out-standing property of the heart is its remarkable adaptation to the amount of work required of it. Krogh has shown that in the normal individual at rest, the left ventricle pumps out 3 litres of blood per minute; during moderate muscular exercise this quantity may rise to 12 litres; or in an athletic individual undertaking very hard work to as much as 21 litres per minute. This last figure means that the heart can pump the total blood contained in the body round the whole circulatory system six or seven times in the course of a minute and this in spite of the fact that during the muscular exercise the arterial pressure against which the heart has to work is considerably higher than in condition of rest, being equivalent to about 110 mm. Hg. and in the former to 150-160 mm. Hg. Another important fact from the standpoint of the treatment of cardiac disease is the care taken to see that the heart muscle is properly nourished. Starling has shown that the greater the work the heart has to do, the greater the amount of blood flowing into the coronary arteries to supply the muscles, etc. For example:

With an arterial pressure of 84 mm. Hg. the coronary arteries received 40 c.c. of the 851 pumped from the left ventricle. At 170 mm. Hg. pressure 117 c.c. of 860 c.c.; at 208 mm. Hg. 260 c.c. of 860 c.c. went to the heart muscle. This means that the supply of blood to the heart is in proportion to the work it has to do. The blood supplies the oxygen as nutriment necessary to furnish it with energy. This of course gives a foundation to work on in advising increasing exercises—always keep in mind the fact that the muscle tone is sufficient.

This brings us to the third point namely, that property of the heart muscle called "Tone". It is perhaps best described as "the physiological condition or fitness of the muscle fibre and its measure. The energy set free per unit length of muscle fibre at each contraction of the heart muscle". A heart in good condition, *i.e.*, one with a good tone, will carry on a large circulation against a high arterial pressure and nearly empty itself at each contraction, while a heart with a defective tone, as is the case when it is tired, can carry on the same circulation but only when its fibres at the beginning of contraction are much longer, *i.e.*, when the heart is dilated.

These physiological properties help one greatly in obtaining a comprehensive understanding for the handling of cardiac cases. The fact that exercise increases the blood supply to the heart, giving it food and removing waste material at once gives the suggestion that the heart should be exercised in proportion to its ability to respond. Gradually increasing the exercise should increase the efficiency of the heart by increasing the muscular tone. It also follows, that the heart muscle fibre

cannot be physiologically fit while the infective process is still present.

There are two or three methods for gauging the tone of the heart muscle. At present a great deal of work is being done on the estimation of the vital capacity of the lungs as a measure of heart efficiency. With this method we have had no experience; it necessitates an expensive instrument. Equally reliable information may be obtained by studying the blood pressure or the pulse after exercise. The effect on the blood pressure is a little harder to estimate as one has to keep the instrument attached and still have the patient with sufficient freedom to permit exercise. This may be accomplished by having the patient lying down, with the instrument ready applied to the arm, the exercise consisting of movements of the legs. Normally, the pulse rate increases, of course, during the exercise, returns to the same rate as before the exercise, by the time two minutes have elapsed. For example—say a patient has normally a pulse rate of 80—at the end of some standard exercise test it may reach 110, may be 85 or 90 at the end of the first minute, and normal at 80 at the end of the second minute. On the other hand, a patient with cardiac disease in which the muscle tone is poor, the pulse may not return to its former rate for 4 or 5 minutes after the test. This gives a ready method for recording the progress of a patient.

As to the test of exercise—a common one is having the patient with arms fully extended over the head, touch the floor ten times. In counting the pulse, the 1st quarter minute after the exercise is taken. Similarly, the last quarter of the first and second minutes are taken to give the pulse rate at that time. Besides the action of the pulse—flushing of the face, degree of dyspnoea during the exercise, and the fatigue after are all carefully watched. The more severe test such as stair climbing, dumb-bell exercise may be used in judging the efficiency of the heart under stress.

Making use of these measures just outlined, we are accustomed to classify our classes as 1st, 2nd and 3rd degree.

The first degree cases are those showing signs of heart disease but with no symptoms referable to the heart—they do not know they have cardiac trouble. The children play and carry on as normal children. Their exercise tolerance is normal.

The second degree cases have physical signs and symptoms referable to the heart. The exercise tolerance is diminished. On exertion they have dyspnoea, flushing and palpation.

The third degree have physical signs and symptoms of cardiac failure (decompensation), exercise tolerance absent.

At the Hospital for Sick Children in a group of 76 children able to attend the out-patient Cardiac Clinic—70% are cases of first degree, 24% of second degree and 6% of third degree.

As you will judge, it is the first two types of cases only in which one may hope to have much success in increasing their cardiac efficiency. In these two groups, the removal of any physical defect or focus of infection followed by proper hygienic measures (good food, fresh air) combined with proper graduated exercise under supervision will bring excellent results.

SOME PROBLEMS OF DEVELOPMENT

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IT is so much the ordinary thing for a fertilized egg of a given species of animal to develop into a representative individual of that species that any marked departure from that result is looked upon as an abnormality. So powerful are the internal forces directing development that a proper environment—temperature, moisture, etc.—and sufficient nourishment are looked upon rather as necessary conditions than as containing directive forces. If these conditions are not fulfilled within certain limits, development is impossible; as these limits are approached, various abnormalities arise. Even in these cases it is not possible to connect immediately the unusual condition and the abnormal result. It appears rather that the unusual condition has disturbed the balance of the various internal forces and that the abnormality is the result of lack of harmony in their action.

What are these internal forces? Often they are spoken of as the "heredity" of the egg. As agents through which this heredity becomes manifest there is first the cytoplasm of the egg with its structure and chemical composition so complicated that in no two kinds of eggs, perhaps in no two eggs from even the same individual is it quite the same. For it is allowable to apply to the egg the dictum uttered with regard to the cells of the body: "Every cell of the body has a chemical character in common with every other cell of that body and also in common with the body fluids; and this particular chemical group differs from that of every other individual of the species and to a still greater degree from that of any individual of another group or species."[1] Of perhaps even greater importance is the chromatin of the nucleus, in complexity of constitution and of possibilities a cosmos in itself. Abridging H. F. Osborne's characterization it may be described as far more stable than the surface of the earth; at once most conservative and most progressive, recording the body form of the past, meeting the emergencies of the present, and continually giving rise to the new.[2]

But the large number of ascertained facts and laws of heredity must not tempt us to be too easily satisfied and let the use of that impressive word cover a great field of ignorance. Admitting the control of heredity some analysis of the forces which are its servants may be attempted. If they are well understood perhaps some direction may be given them from without and the course of development modified. The ultimate goal would be so to direct development that the result would be an improvement upon that which heredity alone would have produced. If that seems too remote we may at least hope to learn to avoid conditions that will tend to the production of abnormalities of an injurious kind. That such are continually being produced is unfortunately true.

This article makes no attempt to deal with all the forces involved in development; it aims only to suggest minor problems, and lines of approach through which attack may be made on the main problem. Its illustrations are taken from but two areas of the field; one of very early development when the body as a whole and its chief organs are in process of formation, and one later when its tissues are developing.

I.

In the eggs of many of the lower forms of animal life the quantity of yolk is very small. Beginning their development, such eggs divide into two, and then into four cells. If at this point the eggs are shaken in water the result is often to separate entirely the cells from one another. An abundance of yolk adds to the mechanical difficulties of the separation but even so yolk-laden an egg as that of a salamander or frog may be successfully divided by means of a fine hair tied around the egg in the first cleavage furrow and gradually tightened. In a large proportion of the eggs treated as above each of the cells so separated continues its cell division; however the result is not to form a fragment of an embryo but a whole embryo one half or one quarter the normal size.[3] In some cases this kind of result may be attained after the egg has divided into eight, or even into sixteen cells.[4] The converse of this, the coalescence of two eggs in an early stage of development to produce one embryo of double size, has also been obtained experimentally.[5] Such results are rather disturbing to the accepted ideas of the individuality of the body and its continuity throughout development.

Evidently in normal development the cells first formed do not exercise to the full their powers. Every one of the cells is clearly restrained by its companions. How is this restraint exercised? Is it through so simple a thing as stimuli arising from mere physical contact? Sever the contact, stimuli cease to arise, restraint ceases. Or does each cell produce a substance that diffusing into the other cells limits for each of them their possibilities of development to the subordinate part each must play in the whole? In plants this seems to be the way in which an active growing-point,—a bud—inhibits the development of others nearby.[6]

Or is this only a special case of a general power possessed in varying degree by all living organisms at all periods of their development? Consider the following series of experiments.

In amphibian eggs the yolk is of greater specific gravity than the protoplasm; it is massed chiefly in the part of the egg opposite to the greater part of the protoplasm; consequently the egg is weighted toward the end of one axis. Since under natural conditions the egg is free to rotate this becomes the vertical axis; the protoplasm is chiefly above and the yolk chiefly below. By the first cleavage these two parts are divided equally between the two cells resulting. If now the egg is pressed lightly between two sheets of glass it can no longer rotate and may be turned and kept with the yolk-laden part uppermost and the protoplasmic part beneath. The semi-fluid nature of these substances permits the differing specific gravities to produce their natural effect; the yolk sinks slowly, the protoplasm streams upward, and at the price of reorganizing the distribution of materials within the egg the natural relation of the parts is reassumed and development proceeds. But with the result that each of the two cells produces a whole embryo.[7] This result would seem to remove from consideration as directive forces the possibilities of stimulus from contact and of the diffusion of substances from cell to cell. It would rather appear that the reorganization of the egg had set free in each cell a power that was suppressed so long as each cell was but one-half of an organization previously existing—the undivided egg.

The eggs of some species of animals (*e.g.*, Dentalium) even before

development begins show a differentiation into regions marked by a special color or texture. In later development each such region can be followed and be seen to give rise to definite organs. If one of these regions is experimentally removed before development begins, the embryo when formed will lack the organs that would have developed from it.[8] Here evidently there is completed very early within the egg an organization so rigid that materials cannot be redistributed to repair losses.

Blastulae of Asterias cut in two will form complete but dwarf larvae; gastrulae the same; also larvae so far advanced as to contain an intestine, but only if each piece contains a part of the intestine. If the cut is so made that one piece contains no intestine the embryo is completed so far as the form of the body is concerned but contains no intestine. Here organization of the egg is much more slowly attained but eventually becomes as rigid as in the previous case.[9]

It is customary to think of the process of development as being accompanied by a distribution of materials among the cells as they are formed. Once the materials necessary for the formation of an organ have been given over to the cells forming that organ the loss of those cells is irreparable. But so long as the materials are distributed more or less throughout the egg the loss of any one group of cells can be made good. In Dentalium this kind of distribution occurs even before development begins, in some other kinds of eggs it is deferred until comparatively late in development, but the difference is one of time-relation, not one of process. An extension of the same idea may be made to afford an explanation of the healing of wounds and of the varying degrees of regeneration of lost parts that may accompany healing in different animals.

Still less tangible are the forces at work in such cases as the following. By shaking in water certain eggs, which have developed to the point of consisting of eight cells, all the cells may be caused to lie in one plane. When the egg is again at rest the cells begin moving in reference to one another and in many cases restore the original grouping and proceed to normal development.[10] A similar process may be seen later on in development. For instance when mesenchyme cells are first formed shaking the eggs will displace these cells into abnormal positions. After a period of rest most of them will be found to have moved to such places as they would have occupied, if undisturbed, in the stage of development then attained. Further development then proceeds normally.[11] By driving segmenting eggs repeatedly back and forth through a narrow opening the cells may be forced into a linear row, the larger cells occupying the central part of the chain. After a period of rest the original form of the cluster is restored although every cell does not necessarily recover its original position. Further development proceeds normally.[12] In adult hydroids[13] and some worms[14] portions cut from the body if not too small will become moulded into a new individual, and this by rearrangement of the tissues already existing, with little or no addition of material formed anew by cell-division.

This power of living matter is referred to as *regulation* to distinguish it from *regeneration* where growth and the production of new tissue are prominent features. The difficulty of resolving it accurately into forces already known is one of the chief bases of "vitalistic" theories of life, theories having this in common that they assume a directing force in

living matter over and above the physical and chemical forces at work elsewhere in nature. Such an appeal to the unknown can hardly be regarded as scientific and is of doubtful value. On the other hand an appeal at large to the powers of surface and internal tensions, ions, catalysts, emulsions, and polyphase colloidal solutions, things whose powers and interactions have not as yet been determined with exactness is no less an appeal to the unknown. The very basis of the appeal is that although what is at present known about them cannot explain the result, the explanation will lie in what is as yet unknown. This cannot be regarded as a satisfactory answer but it does contain suggestions for further work.

II.

Turning now to a consideration of abnormalities of development we find the situation more satisfactory for there is at hand a hypothesis which if not capable of rigid proof at least harmonizes what are otherwise discordant results and affords a rational basis for planning further experimental work. In general the milder degrees of abnormality are due to development having failed to run its complete course in the case of one or more organs; more serious are cases where organs are only rudimentary, perverted, or entirely suppressed. Twins more or less united constitute a third group. Where one of the two individuals is less developed than the other a kind of parasitism occurs. In its more extreme degrees the reduction of the smaller, parasitic individual in size, in organs, and in organization may result in complete loss of apparent individuality and what is in reality a twin becomes a mass of tissue difficult to distinguish from a true neoplasm.

Such results are frequent when the physical and chemical conditions under which development proceeds have been varied from what is normal. High or low temperature; exposure of the eggs to the action of different chemicals, and these in solutions of different strengths; withholding oxygen for a time: these and a few other means of like nature have all been extensively used. Along these lines a great variety of causes may all produce the same defect. For instance that abnormality of the spinal cord known as "spina bifida" has been produced by almost all the agents commonly used in such experimentation. In other experiments the same causes have produced other defects. "Cyclopia" the union of both eyes into one placed in the middle line of the face is especially common. Again using the same means the result has at times been twins, more or less complete, and usually more or less united. It remained for Prof. Stockard of Cornell to detect the factor the recognition of which establishes order among the seemingly chaotic results. What follows on this point is based on his publication but no description of his extensive experiments in confirmation is attempted.[15]

Since like other living organisms the eggs are adjusted to their normal environment during development it is not surprising to find that any marked departure from it is in the nature of an injury, a check to the course of development. It is noticeable that normal development does not proceed at an even pace in all parts of the egg. In general the appearance of the first trace of an organ is preceded and accompanied by more rapid cell division and cell movement at its site than elsewhere. Metabolism is there more active and the cells in a more impressionable state than are the other cells of the egg. If now development is checked they will suffer more than the average cell and when the interference

is removed they cannot recover their original superior speed of development. The allotted time during which they should dominate development passes and they cannot take full advantage of it. Henceforth they will be more or less restrained by the initiation of other organs and the one they should have formed will be imperfect or entirely suppressed. Consequently which particular organ shall suffer from an experiment depends not so much on the experiment itself as on the stage of development at which it is performed.

It is seemingly a paradox that the same process which in one case partly suppresses development should in another case result in the production of two individuals from one egg. Again the explanation lies in the stage of development attained at the time of interference. In the first experiments referred to in this article we saw how the occurrence of a process suppresses possibilities of a similar process being repeated; a general condition typified by the growth of one bud suppressing that of others nearby, others that will begin growing should the original one be destroyed. It has been observed that the determination of the axis of the body of the future embryo is preceded by heightened activity of a small group of cells in that axis. If these suffer such a check that they cannot establish priority for the axis they would determine, other groups may succeed in establishing other axes almost simultaneously and an individual forms around each. Usually but not invariably these are but two in number. Since they are both connected parts of the same egg it is not surprising to find often the two bodies joined to a varying extent. For the same reason a competition for the nourishment available ensues and since all the factors favouring growth can rarely be divided with absolute equality between them one individual will usually outstrip the other, the latter may even be so poorly developed as to appear a parasite upon the larger.

III.

As development advances the number of cells composing the body increases and gradually groups of cells take on characters that distinguish them from other groups that are differentiating along quite other lines. The result of this is the production of the tissues of the body. In the limbs, for instance, muscular tissue, ligament and bone arise from the descendants of cells that were of similar appearance and of common origin. In this process of differentiation some of the results seem to be due to the mechanical effect of active growth in one area upon neighboring areas. Typical examples of such development are the muscular coat of the intestine and the skeleton and muscles of the limbs.[16]

In its earliest form the intestine consists of two elements, an inner epithelial tube, and fitted over it accurately an outer tube of mesenchyme. At first epithelial growth outstrips that of the mesenchyme, and the diameter of the inner tube increases rapidly. This distends the mesenchyme and causes an elongation of many of its cells, their long axes becoming concentric with the circular outline of the cross-section of the intestine. Until now these mesenchyme cells have resembled all the rest but under the stimulus of this stretching they rapidly take on the character of muscle, developing into the circular subdivision of the muscular coat. This muscle in turn exerts a pressure upon the epithelial tube which can no longer expand in diameter as readily as before; its growth consequently becomes chiefly longitudinal. At once the mesen-

chyme cells of the more outward parts feel the stress and become elongated in a longitudinal direction. As before this seems to supply the stimulus for the transformation of what were unspecialized mesenchyme cells into muscle. Thus arises the longitudinal subdivision of the muscular coat; the circular subdivision is not affected, having already proceeded far enough in development to ensure its completion. Similar action and reaction of growing portions of the mesenchyme of the limb-bud, have been detected in the successive development of the central blastema, its bounding membrane (eventually the periosteum), the joints, the surrounding muscles and the final form of the bones.

More subtle stimuli than the grossly mechanical ones just described are frequently if not invariably involved. Experiments in transplanting organs have clearly pointed to this conclusion even if they have not revealed the exact nature of the stimuli.

One typical series of such experiments involves transplanting the anterior limb while it is yet a mere bud, or sometimes a portion of the spinal cord.[17] Normally in the salamander larvae used in these experiments the anterior limb receives its nerve supply from the third, fourth, and fifth spinal nerves. These unite to form a brachial plexus of simple but constant pattern and from it branches arise which run a constant course and reach each a particular and constant distribution. The number of nerve cells in the third segment of the spinal cord is greater than that in the fourth and this in turn greater than that in the fifth. The anterior limb-bud may be removed and grafted back one, two or more segments posterior to its normal position. In all these positions it will grow and develop its normal muscles and pattern of nerve distribution to them. But the nerves that now enter into the brachial plexus are not the normal ones unless the bud has been grafted back not more than one or two segments posterior to its normal position. If grafted back more than three segments posterior to its normal position the brachial plexus will include the sixth or more posterior spinal nerves which normally supply abdominal muscles. But within the limb, nerve and muscle pattern is normal.

Evidently conditions within the limb determine how the nerves shall branch, the course of the branches and to which muscle each branch shall be distributed; for this is the same even if the brachial plexus includes nerves usually distributed to abdominal muscles. The pattern of the peripheral nervous system of these larvae—and presumably of all vertebrate animals—consequently is not hereditary in the sense that each nerve fibre as it grows follows a hereditary pathway to a definite and hereditary termination. But the pattern is hereditary in the sense that corresponding nerve fibres in all normal larvae meet, during their growth, with the same influences and accordingly arrive at corresponding destinations. But if this is true why should the normal nerves continue to enter into the brachial plexus if the limb-bud is moved only a short distance posteriorly? A possible answer is suggested later.

When as above the limb muscles receive their nerve supply from spinal segments that normally supply only abdominal muscles each segment controls a mass of muscle much greater than is normal to it, but the nerve cells are not increased in number as a result. Functional demand has not acted as a stimulus to produce more nerve cells than usual. If the limb-bud is not disturbed but the spinal cord of the third,

fourth, and fifth segments is removed and after being reversed is grafted back, healing soon restores the continuity of the spinal cord, but its present third segment was originally its fifth and *vice versa*. The nerve that now grows from what is in reality the fifth segment assumes all the characters of the normal third nerve, while the true third nerve assumes the place and pattern of the fifth. But this time the number of nerve cells in the fifth segment, now in the position of the third, is greater than the number in the true third segment, now in the position of the fifth. If segments three to five of the spinal cord are removed and replaced by a piece of cord from a more posterior level the results are exactly the same as those just described. Evidently a segment of the spinal cord has the number of nerve cells in it determined by the level it occupies in the developing cord and not by its initial position, or even by the functional demands made upon it. There is evidence that more of the nerve fibres descending through the cord from the brain end in the third spinal segment than in the fourth, and more in the fourth than in the fifth. It is probably the number of stimuli coming through them that determines the extent of nerve cell production in the different segments of the cord.

It has been suggested that an electro-chemical force produced by a spontaneous activity in cells, muscle-fibres, etc., guides toward them a growing nerve fibre. This would explain the innervation of transplanted muscles. Should certain nerve fibres—say those from the third spinal segment—be more sensitive than others to the electro-chemical stimuli proceeding from a certain mass of tissue—say the anterior limb-bud—there is afforded a basis for understanding why, although other nerves may replace the third spinal in the brachial plexus, none will do so unless the limb-bud has been removed to a distance from the third spinal nerve too great to permit the influence to be felt by its fibres.

Along lines similar to these is being waged the campaign to unravel and identify the forces concerned in development and growth. Facts in enormous number are being established, hypotheses are constructed and tested; some of them are so illuminating of the facts, so profitable as a basis for further work, and so uncontradicted by what is established that they may be dignified by the name of theories. But it is not to be expected that rigid, final proof of these theories can as yet be forthcoming. Such studies may well lessen the sense of mystery that surrounds living organisms but they increase the appreciation of the wonder of them. Each part of every organism appears the seat of so many forces each acting on so minute a stage, all controlled and harmonized. Does the secret lie in their mutual reactions and interactions, or does something external, without adding to or subtracting from the total energy involved, direct them? So far the light thrown on the problem serves to demonstrate its immensity rather than to reveal its centre.

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(EDWARD JENNER 1749-1823)

By

A Graduate

LAST year was the centenary of the death of Jenner and was recognized as such by many of the scientific societies throughout the world. The most interesting celebration from an international viewpoint was that held in Paris, when the British and continental scientists paid homage to the memory of one of humanity's greatest benefactors.

He was born in a country village and his father was a preacher—a combination of environment and heredity that has produced many men of science and letters. He was the third son of Rev. Stephen Jenner—a vicar at Berkeley in Gloucestershire..

At the age of 13, he was apprenticed to Messrs. Ludlow, a firm of surgeons at Sodbury, near Bristol, with whom he remained six years.

It was during this apprenticeship that a country girl who had come to his master's house for advice, casually remarked, "I can't take smallpox, I have had cowpox". Such was common gossip among the dairymaids of Gloucestershire, but no one thought it worthy of investigation. Here again history repeats itself. The teachings of the grandmother, the quack, "the adjuster", the faith healer should not be treated with entire contempt and disdain. Withering discovered digitalis because of the recipe of "an old woman in Shropshire who cured dropsy". Our two specifics—quinine and mercury—have the same ignominious origin.

A Lasting Impression

This incident about cowpox preventing smallpox made a lasting impression upon the young lad . . . to be mused over, . . . discussed with friends, . . . set aside, . . . and returned to later in life. He had been inoculated with smallpox at the age of eight, and had undergone a very strenuous preparatory treatment—he was bled, purged and then starved for six weeks. It is possible that the memory of this severe experience quickened his interest in the traditions about cowpox and smallpox. At

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any rate, he decided to investigate the problem, when an opportunity presented itself. Later, in 1796, Sarah Nelmes, a dairymaid, consulted him about an attack of cowpox. Why not try out the experiment he had planned? He inoculated James Phipps, a lad of eight, with the pus from Sarah's arm. . . . What would happen? Would Jimmie be immune to smallpox? How long before immunity would develop? (There were no courses or examinations in Immunology in Jenner's day.) At last, after waiting six weeks, he decided to apply the crucial test. He inoculated Jimmie with the pus from a smallpox patient. "If he is not immune he will develop smallpox",—but he did not develop smallpox. He then exposed him to smallpox but Jimmie would not or could not take smallpox. He repeated his observations on other patients with always the same result. He now knew that vaccination with cowpox (vaccinia) prevented smallpox. He continued his researches for two more years before he published his results—(Harvey took ten years).

This is in decided contrast to these days of struggle for priority and honors. The original volume is difficult to secure but one can buy very cheaply the beautiful facsimile published last year. There is a copy available in the Library.

Lack of Recognition

"A prophet is not without honour save in his own country." In England, Jenner and vaccination were ridiculed—caricatured—denounced by the pulpit as diabolical. But, how differently did the stranger treat this discovery! The French government offered vaccination gratuitously. Napoleon, even though at war with England, granted Jenner special favours. The Empress of Russia decreed that the first child to be vaccinated was to be named "Vaccinoff", and the child was to be educated by the state. Little "Vaccinoff" became a kind of national hero, and was conveyed to St. Petersburg in one of Her Majesty's Imperial coaches. Holland, Italy, Spain, Germany, and even far off Japan, all enthusiastically accepted Jenner's discovery.

Disappointed in Love

Jenner at the age of 21 had become a house pupil of John Hunter in London. Later he returned to his home village, to become "just an ordinary general practitioner"; he fell desperately in love, but "something happened". (This is a clinical syndrome, not unknown to final year Meds.). He wrote to Hunter for consolation and advice. As was to be expected he received little of the former but plenty of the latter. "Let her go" wrote Hunter, "Never mind her. I shall employ you with hedgehogs. . . . I want you to get a hedgehog at the beginning of winter and weigh him; put him in your garden and let him have some leaves, hay, etc." The remedy seems harsh to a tender youth but it was good psychotherapy. Anyhow it produced results. Ten years later, when more mature and discriminating, he was happily married to Catherine Kingscote.

General Practitioner

Jenner went to London hoping to find a larger field of usefulness. The country doctor received scant recognition, and he decided to go back to his native village. He is once again the beloved general practitioner. Here he continued his studies of bugs and bees and beetles until his death which occurred in February 1823.

RECIPES FOR THE DIABETIC

As used in the Toronto General Hospital

Printed through the kindness of the Head Dietitian, Private Pavilion, Toronto General Hospital.

Teaspoon=Tsp. 3 Tsp.=1 Tb.
Tablespoon=Tb. 16 Tb.=1 C.
Cup=c. 4 C=1 Qt.
f.g.=Few Grains.

30 Grms.=1 Oz.
15 Grms.=½ Oz. or 1 Tb. liquid.

To Wash Bran

Buy unprepared feed bran. Sift to rid of fine starch. Half fill a cotton sack, tie firmly at the top, leave under running water turning or kneading every 15 minutes, or wash through 10 to 12 waters, or till water comes quite clear of all starchy appearance. Wring as dry as possible, spread in pans. Dry in a slow oven stirring occasionally.

Thoroughly dried bran may be stored indefinitely.

Bran Wafers

3 c dry washed bran ½ tb salt
4 tb India gum hot water

1 tsp each of cinnamon and nutmeg and 1 grain saccharin may be added if desired.

Method—Mix dry ingredients thoroughly, add hot water to make a soft dough. Spread in thin layers on a baking sheet greased with mineral oil. Cut in squares. Bake in a slow oven until dry and crisp.
No food value.

Bran Muffins

⅛ c dry washed bran. 1/3 egg.
2½ tb Cellu flour. ½ tsp. India gum.
½tsp baking powder. 1½ tb mineral oil.
f. g. salt. warm water.

Saccharin if desired.

Method—Mix dry ingredients thoroughly, add mineral oil, egg and sufficient warm water to make a batter that will drop from the spoon. Bake in small muffin tins in a slow oven till dry.
Food value P2. F2.

Cellu Bran Wafers

3 c dry washed bran. 1 tb baking powder.
1½ c Cellu flour. 1½ tb mineral oil.
3 tb India gum. 2 grains Saccharin.

hot water.

Method—Mix dry ingredients thoroughly. Add mineral oil and finish as for Bran Wafers, may be spread somewhat thicker, 3/8 in. These may be spiced, flavoured with caraway seeds, or nuts may be added, providing of course, their food value is calculated.
No food value.

Cellu Pie Crust

¼ c Cellu flour.
2 tb dry washed bran.
2 tsp India gum.
f.g. salt.
saccharin.
½ tb mineral oil.
1½ tb warm water

Method—Mix as for Cellu Bran Wafers, adding sufficient warm water to make a dough. Mould in muffin tins. Bake in a slow oven till dry. This recipe makes two pie crusts.
No food value.

Pumpkin Pie

80 to 100 grams pumpkin.
salt.
cream (from allowance).
spices.
saccharin.
egg.

Method—To the amount of pumpkin stated in diet add 1 tb cream, from day's allowance, and the white or the yolk of an egg may be added. Season with salt, spices and saccharin, pour into a crust and bake. Any fruit in diet may be used in place of pumpkin.
Food value with egg yolk P2. F6.
Food value with egg white P4.

Diaprotein Bread

1 measure Diaprotein flour.
f.g. salt.
2 eggs.
2 tb water.

Method—Beat egg yolks till quite thick, add water and fold into stiffly beaten white of egg, then carefully add the flour. Do not stir or beat, Bake in a moderate oven increasing heat at the last. Loaf must have a firm crust on it or it will lose its shape. Average weight of loaf 140 grams.
Food value loaf, P 43.5, F 13.5. Food value of 10 grams, P 3.1, F .9.

Lister Flour Bread

1 pkg. Lister flour. f. g. salt 3 eggs.

Method—Combine and bake as for Diaprotein Bread. Average weight of loaf 160 grams.
Food value of loaf P 59.9, F 18.3.
Food value of 10 grams P 3.7, F 1.1.

Soy Bean Muffin

90 grams Soy bean flour.
2 eggs.
¼ ts soda.
120 grams buttermilk.
2 tsp baking powder.
saccharin.

Method—Beat egg yolks and add buttermilk to which soda has been added. Mix other dry ingredients and stir in. Lastly fold in stiffly beaten egg whites. Bake in a moderate oven in muffin tins 25 to 30 minutes. Makes 10 muffins.
Food value of 1 muffin P 5.4, F 2.7, C .6.

Cheese Crackers

Use Cellu bran wafers. Grate cheese about ⅛ in. thick on them and brown in a moderate oven.

Macaroons

1 egg white — 10 grams blanched almonds.
¼ grain saccharin or a few drops of liquid.

Method—Beat egg white stiff, fold in the nuts chopped fine, add saccharin, drop in spoonsfull on waxed paper and brown in a moderate oven.

Food value P 6.1, F 5.4, C 1.7. Food value of each P 1.5, F 1.3, C .4.
This recipe makes 4 macaroons.
Or 10 grams California walnuts may be used.
Food value P 5.8, F 6.4, C 1.3. Food value of each P 1.4, F 1.6, C .3.

Peanut Cookies

1 egg. — 30 grams butter.
1 tb water. — 25 grams Soy bean flour.
grated rind of 1 lemon, 10 grams chopped peanuts, ¼ tsp baking powder.

Method—Hard cook egg, cool and grate. Cream butter and add egg, water and lemon rind, cream well. Add flour and baking powder. Drop in 12 on a baking sheet and bake in a moderate oven till firm.
Food value of 1, P 1.5, F 3.3.

Bran Griddle Cakes

1 c dry washed bran. — 1 egg.
1/3 tsp salt. — 1 tb fat.
½ tsp baking powder. — ¼ c water.

Method—Mix dry ingredients, add water and well beaten egg. Drop in spoonsfull on a hot griddle greased with mineral oil.
Food value P 6. F 18.

If egg and fat are used from diet sheet food value need not be counted.

Cellu Griddle Cakes

4 tb Cellu flour. — 1 egg.
½ tsp India gum. — ¼ c water.
1/3 tsp baking powder. — f. g. salt.

Method—Prepare as in previous recipe.
Food value P 6. F 6. — May be substituted for 1 egg.

Maple Syrup Substitute

2 to 4 grams agar. — 1 c hot water.
saccharin. — 1/3 tsp Mapeline extract.

Method—Dissolve agar by boiling in water. Strain and add saccharin and flavouring.
No food value.

Junket

1/3 c 80 grams milk. — 1/12 Junket tablet.
flavouring. — 1 tb lukewarm water.
saccharin

Method—Heat milk to blood temperature or 100°F and pour onto the Junket tablet which has been dissolved in water. Flavour, stir well and pour into a mould. Let stand in a warm place till set.
Food value P 2.5, F 3, C 4.
May serve with bran muffins and have the value of a baked custard.

Baked Custard

1/3 80 grams milk.
1/3 egg.
flavouring
f. g. salt.
¼ grain saccharin or
a few drops of liquor saccharii

Method—Beat the egg and add flavouring, salt, saccharin, and scalded milk. Pour into a custard cup. Place cup in a pan containing hot water and bake in a moderate oven.
Food value P 4.5, F 5, C 4.
May treble the recipe: 1 egg and 1 cup milk and make three custards.

Purity Custard

1 egg white
f. g. salt.
1/3 c 80 grams milk.
vanilla or nutmeg.
saccharin

Food value P 6.4, F 3.2, C 4.

Custard Sauce

1/3 c 80 grams milk.
1/3 egg yolk.
saccharin.
1/3 tsp flavouring.

Method—Combine as for baked custard. Cook in the top of double boiler until mixture coats the spoon, remove, add saccharin and flavouring.
Food value P 3.1, F 5.2, C 4.
Served with Bavarian cream or Snow pudding. Food value P 4.4, F 5, C 4.

Floating Island

1/3 c 80 grams milk.
1/3 egg yolk.
1/3 egg white.
1/3 tsp flavouring.
saccharin.

Method—Combine as for custard sauce reserving egg white. Turn into a mould and pile stiffly beaten egg white on top. Set in the oven to brown. (Or egg white may be folded in as in Spanish cream).
Food value P 4.5, F 5, C 4.

Bavarian Cream

½ tsp agar.
1/3 c boiling water.
1/3 egg white.
½ tsp lemon juice.
and grated rind
saccharin.
1 tb cream (from allowance).

Method—Dissolve agar by boiling in water, strain, add lemon and saccharin, fold in the beaten egg white and the whipped cream, and turn into a cool wet mould. Orange juice or any diabetic flavouring may be used in place of lemon.
Food value P 1.3.
Served with milk, soup or custard sauce. Food value P 4.5, F 5, C 4.

Orange Snow Pudding

½ ts agar.
1/3 c boiling water.
1/3 egg white.
1 tb orange juice.
grated orange or lemon rind.
saccharin.

Method—Prepare as for Bavarian cream. May vary recipe by using lemon juice or any diabetic flavouring. Food value P 1.3.
Served with milk soup or custard sauce. Food value P 4.5, F 5, C 4.

Spanish Cream

Method—Use the same recipe as for baked custard reserving egg white and adding ¼ tb agar and ¼ cup boiling water. (Boil till dissolved). Combine as for custard sauce, add the strained agar and continue cooking in the top of double boiler till mixture is thick. Cool slightly, fold in the stiffly beaten white of egg, and pour into a cool wet mould.
Food value P 4.5, F 5, C 4.

Coffee Cream

½ tsp gelatine.
5 tb coffee.
Saccharin.
1 egg.
60 grams cream.
60 grams hot water.

Method—Soak gelatine in coffee, add boiling water, stir till dissolved, add to beaten egg yolk and cream. Finish as for Spanish cream.
This recipe makes 2 desserts.
Food value of each P 4.3, F 12.6, C 1.

Gelatine Dessert

1 tsp gelatine.
1 tb cold water.
½ c liquid.
Saccharin.
flavouring

Method—May use the allowance of fruit calculated in diet, either as juice or as a fruit with water added. Water with diabetic flavouring.
Food value P 2.6.

Jelly Dessert

1 pkg. D. Zerto.
10 grams almonds.
½ c boiling water.
20 grams 10 per cent. fruit.

Method—Pour boiling water over powder and stir till dissolved. Line a mould with fruit and pour jello into it. Set in a cool place till firm. The nuts may be dropped and served over the top, with part of the cream allowance whipped; or may be salted, using mineral oil.
Food value P 4.1, F 5.4, C 3.7.

Jelly Whip

Follow recipe for jelly dessert and when jelly begins to set, beat and fold in 1 tb whipped cream, from allowance. Nuts may be served as desired.
Food value P 4.1, F 5.4, C 3.7.

Cranberry Jelly

2 grams gelatine.
1 tb cold water.
60 grams cranberries.
saccharin.
2 tb boiling water

Method—Soak gelatine in cold water and dissolve in boiling. Add cranberries which have been cooked and put through a ricer. Turn into a mould and set in a cool place.
Food value P 1.8, C 6.

Agar Jelly

2 tb agar.
4 c boiling water.
saccharin.
flavouring.
colouring

Method—Add boiling water to agar and boil until dissolved. Flavour and colour and pour into wet moulds. Grated rind of orange, lemon, coffee, strained cocoa shells or any diabetic flavouring may be used.
No food value.

Mousse

60 grams (2 oz.) 32 per cent. cream.
flavouring.
¼ grain saccharin.
½ tb agar-agar syrup.

Method—Whip cream, add flavouring, fold in hot agar, put in a covered container and pack in ice and salt 2 to 3 hours. May use any diabetic flavourings, coffee, or part of the day's fruit allowance. May be crushed and added to the whipped cream, or serve with a sauce.
Food value P 1.4, F 19.2, C 2.1.

Twice-Cooked Apples (10 per cent. fruit)

Method—Peel and cut sour apples into eights, add 1 pint of cold water to each apple, bring to the boiling point. Drain, add cold water and again let boil. Drain and finish cooking in the top of double boiler. May be flavoured with a little lemon juice and saccharin. Apples cooked this way may be calculated as 10 per cent. fruit.

Thrice-Cooked Vegetables

Method—Prepare the vegetables in the usual way. Place in cold water ½ hour. Add fresh cold water and boil 5 minutes. Repeat this three times, the last time cooking until vegetables are tender. Vegetables may be reheated in a little broth or seasoned with meat extracts or vegex.
No food value.

Stuffed Tomatoes or Peppers

Method—Chop fine or grind the allowance of ham, veal or chicken. Add 60 to 80 grams of celery and cabbage, and 20 grams carrots and onion. Season with salt and pepper, mix well, and moisten with broth. Remove top from tomato or pepper, scoop out centre, and fill with mixture. Put in pan greased with mineral oil, and bake in a hot oven 30 to 40 minutes.

Fried Egg Plant

Method—Pare egg plant, cut in thin slices, weigh the amount calculated in diet, sprinkle with salt, weigh, and let stand ½ hour. Dredge with Cellu flour and fry in mineral oil.

Vegetable Cream Sauce

1 tsp agar-agar.
2 tb broth.
Seasoning.

Method—Dissolve agar in broth, strain and season with salt and pepper, onion juice or chopped parsley may be added. Add ½ to 1 tb cream from day's allowance.
No food value.

Broth

1 lb. meat and bone.
3 c cold water.

Method—Chop meat and bone, soak ½ hour in cold water. Simmer 2 to 3 hours in the same water. Strain, season and serve.

Milk Soup

1/3 c 80 grams milk. 1/3 egg yolk.
Broth. 5 grams corn or peas.

Method—Heat the milk and add to beaten egg yolk. Season with salt, pepper, and onion juice. May add ¼ cup broth.
Food value P 3.1, F 5.2, C 4.
Serve in place of broth with Bavarian cream or snow pudding.
Food value P 4.5, F 5, C 4.

Cream Soup

50 grams 5 per cent. Veg. or 25 grams 10 per cent. Veg.
60 grams 32 per cent. cream. broth.

Method—Make a puree of vegetable or chop fine. Season and heat cream and add to hot vegetable. Add sufficient broth to make a serving.
Food value P 1.4, F 19.2, C 3.6.

Chicken à la King

chicken. 10 to 20 grams Pimento.
50 to 70 grams mushrooms. 60 grams 32 per cent. cream.
2/3 tsp India gum. 2/3 c broth.

Method—Stew mushrooms in broth till tender, thicken with India gum, add cream and flavor with pimento, salt and pepper. To this mixture add the amount of chicken cubes which is calculated in diet.

Meat Stew

To the amount of cubed or ground round of beef calculated in diet, add ½ c boiling water and let simmer till almost tender. Then add 80 grams 5 per cent. veg. and 60 grams 10 per cent. veg. and continue cooking till vegetables are tender. Season and serve.

Meat Pie

As for meat stew. When cooked turn into casserole, and cover with a layer of cellu pie crust, and bake until crust is dry.

Cottage Cheese I.

Method—Put 1 quart of sour milk in the top of double boiler. Heat until curd separates out. Let stand for a while. Strain through several thicknesses of cheese cloth and drain till dry. Season with salt and pepper. Chopped pimento and cream from day's allowance may be added.

Cottage Cheese II.

Method—To 1 quart buttermilk add slowly 2 quarts boiling water. Let stand until curd separates out. Drain and finish as in cottage cheese number 1.

Mayonnaise

1 egg. 1 tsp salt.
1 tb mustard. 2 c mineral oil.
1 tsp paprika. 2 to 4 tb vinegar.

Method—Beat egg. Add dry ingredients, continue beating, slowly adding oil. When half oil is added, add vinegar and oil alternately. Dressing should be quite stiff when finished.
Food value P 6, F 6.

SIMPLE TECHNIQUE OF A ROUTINE PATHOLOGICAL LABORATORY

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THERE are a number of things that are essential to the carrying on of proper work in a routine laboratory. Of first importance is a room of proper dimensions and good lighting. A laboratory relegated to the cellar or some dingy corner of the building is neither attractive nor conducive to good work. A room lighted from the north is very satisfactory.

The equipment should be of the best. A defective microscope may deter one from making a correct diagnosis and lead to serious consequences. A poorly cut or an improperly stained section may hinder one from expressing with any degree of confidence an opinion as to the pathological process. It is important, therefore, that adequate accommodation and equipment should be provided.

For the benefit of the pathologist as well as the hospital it is absolutely necessary to keep proper records of the work done. These should include a full description of the gross and microscopic preparations, using a simple language and avoiding the use of diagnostic terms. Place your records in such shape that they may be picked up and readily understood by another.

The record of these findings should then be fyled in such a manner that with proper indexing, they are readily available at all times for further investigation. The work of a routine pathological laboratory is usually divided between a study of material removed at operations and the conducting and investigation of postmortems. The former has a more immediate value involving as it does, at times, the life of the patient. On the other hand the information obtained by postmortem examinations is of immense value to the medical profession in the diagnoses and treatment of their cases. Each case investigated adds something to the sum total of our knowledge. Many cases are of importance from a legal stand-point and require an investigation from a slightly different angle.

The histological examination of tissues, whether from operation or postmortem, represents probably the most important phase of the laboratory work, and necessitates a technique in their preparation of the highest order. Material should be secured as fresh as possible, and great care taken to select the proper blocks of tissue. These should not be more than 5 mm. in thickness, and of a dimension just sufficient to cover the areas required for study. They are then placed in a fixative. The nature of the fixative and freshness of the tissue represent very important factors at times. Some stains are absolutely dependent upon special fixation, others upon the freshness of the material at the time it is placed in the fixative. In the majority of cases, however, this is not so, and tissues, especially if kept cold may be held some hours before fixation without any serious damage to the histological structure. For good staining and histological study, however, tissues ought to be put into a fixative as soon as possible. In each case there should be at least ten times as much fixation as the tissue to be preserved.

By fixation is meant, firstly, the rapid killing of the element so that it may not have time to change the form it had during life and secondly, the hardening of to such a degree as may enable it to resist, without further change of form, the action of the reagents with which it may subsequently be treated. Good fixation is essential to good staining. The action of fixation consists in coagulating and rendering insoluble certain of the constituents of tissues. In the majority of cases the fixing agents enter into chemical combination with certain of the elements of the tissues. Some of the chemicals used in fixatives have the property of combining with certain colouring matters thus affording important stains which could not otherwise be obtained.

For a rapid diagnosis fresh material may be frozen, sectioned and stained very well with a polychrome stain such as Polychrome Methylene Blue. These, however, are not permanent. For permanent mounts one must use material which has been fixed. The choice of fixative to be used is determined largely by the nature of the pathological lesions present or suspected, and on the particular stains necessary for their elucidation. The best general fixative for a faithful preservation of all kinds of tissues, and which also makes possible the use of a variety of staining methods is Zenkel's fluid. In all cases where important cytological studies are to be made, necessitating a variety of special stains Zenker's fixation should be used. For general routine work, however, a 10% solution of formalin is very satisfactory. While this does not permit of the use of any great variety of stains, it is simple to make up, and tissues may be preserved in it as long as desirable. For the preservation of glycogen and sodium urate crystals in the tissues alcohol should be used as the fixative. The tissues after fixation may now be frozen and sectioned on a freezing microtome, but for fine histological work, this is not satisfactory. The material must be embedded in either celloidin or paraffin. The latter is the method used in the laboratories of the Toronto General Hospital and is finding favor in a majority of pathological laboratories. In order to avoid shrinkage of tissue during the process of embedding absolute alcohol and nothing less should be used to remove the water, then fresh chloroform to thoroughly remove the alcohol before placing in the paraffin bath. The most difficult and important part of the whole procedure is the sectioning. This requires, of course, a good microtome, but above everything a knife that has been thoroughly sharpened with utmost care. The slightest flaw in the cutting edge will tear the section.

The sections are then mounted upon slides and, following the removal of the paraffin with xylol and alcohols, are ready for staining.

Staining

Tissues may be stained in bulk. As a rule, however, it is much better to stain them after they have been sectioned; either a frozen section or a paraffin section. The object of staining is to render more prominent the different tissue elements, so that they may be readily recognized and studied, so one uses stains which are selective or differential, by which one tissue-element will be coloured to the exclusion of all others, or at least to the exclusion of other tissue elements which might be confused. These selective stains, which are really micro-

chemical color reactions, enable us to differentiate with ease and accuracy the cellular and intercellular elements, or pathological products, which otherwise look alike. In a short paper of this kind it would be impossible to cover the vast number and variety of stains that are used to-day in a study of the tissue elements of the body. Nor is it possible to give the formulae for their preparation. However, in order to be able to use stains intelligently one should be thoroughly conversant with their ingredients and make up his own solutions. These can readily be found in any book on pathological technique. It is my purpose, therefore, to take up some of the important tissue elements and their products, both normal and pathological, and discuss briefly their staining reactions with the commoner colouring reagents used to-day.

Nuclear Stains

As a nuclear stain, that most commonly used is haematoxylin. Haematoxylin is a dye extracted from logwood. It oxidises very readily, becoming converted into haematein. This latter substance which is the real colouring matter, is an acid body. Combined with appropriate mordants it becomes basic, and can be made to give a powerful nuclear stain. The mordants usually employed are aluminium, iron and phosphotungstin. Of these the first is most commonly used to form alum-haematoxylin. It stains the nuclei a deep blue or purple after the usual fixatives. If the sections are over stained the cytoplasm and intercellular substances may be stained as well. This is not desirable and can be overcome by reducing the staining time or decolorizing with a solution of alum or hydrochloric acid. This will remove the excess stain and leave the nuclei sharply differentiated. Iron haematoxylin, while not quite so convenient as alum haematoxylin, stains the nuclei a very deep purple or black.

There are a variety of aniline dyes which may be used as nuclear stains. Of these methylene blue is the best. With it nuclei are stained blue, showing up with wonderful clearness the finer details of the nuclei under the higher magnifications.

Contrast Stains

Diffuse or contrast stains are used to bring out certain of the tissue elements left uncoloured by the nuclear stains. For this a color contrasting well with the nuclear stain is used. A great richness of detail is obtained with diffuse stains by staining them deeply, then washing out the stain slowly with alcohol. Certain structure have a greater affinity for the stain and by holding them longer stand out a deeper shade than the other structures from which the stain is partially washed out. Of the diffuse stains eosin is the one most frequently used. Eosin is almost constantly used as the contrast stain to alum haematoxylin and methylene-blue nuclear stains. It stains red blood cells, smooth and striated muscle fibres, hyaline, amyloid and fibrin material a deep red colour. The cytoplasm, cell membranes and protoplasmic processes of cells, usually take a delicate pink colour. The fibroglia and collagen fibrils of the fibroblast stain this same colour. The elastic fibrils require a special stain for their identification. Caseous or necrotic material of any kind usually take the eosin stain.

Special Stains

Besides the stains enumerated above there are a variety of special stains, which bring out clearly certain cells or portions thereof, enabling us to readily identify them. In a routine laboratory one is often obliged to resort to the use of these stains to accentuate otherwise doubtful tissue structures. We shall take up the ones more commonly used and give their staining reaction in the tissues.

Most of these stains require special fixatives. Zenker's fluid is that most commonly used and will be the one indicated unless otherwise mentioned.

Van Giemsa's Stain

This is a mixture of picric acid and acid fuchsin. It is an excellent contrast stain to iron haematoxylin. Nuclei are stained a deep purple or black with the iron haematoxylin. Both non-striated and striated muscle fibres and red blood cells stain yellow with the picric acid. Connective tissue fibrils stain an intense red. This makes an excellent contrast stain for the demonstration of fibrous tissue.

Mallory's Aniline Blue Stain

This is a very brilliant and selective stain. Collagen fibrils and reticulum of connective tissue, amyloid, mucus and certain other hyaline substances stain blue; nuclei, cytoplasm, fibroglia fibrils, axis-cylinders, neuroglia-fibrils and fibrin red; red blood cells and myelin sheaths yellow; elastic fibres pale pink or yellow. The various structures do not stain with equal intensity, so that certain ones are brought out with great clearness.

Phosphotungstic Acid Haematoxylin Stain

This, an excellent stain for differentiating certain types of cells, is comparatively easy to handle. With it, nuclei, fibroglia, neuroglia, and myoglia, red blood cells, and collagen fibrils stain a reddish brown, coarse elastic fibrils a purplish tint.

Weigert's Elastic Tissue Stain

Fixation in either alcohol or formalin is preferable although other fixatives may be used. Sections can be stained for several hours. The elastic fibres appear dark blue, almost black on a clear background. A light nuclear stain with alum haematoxylin is advisable and this followed by a diffuse stain like picric acid gives a splendid contrast to the black elastic fibrils.

Scharlach R. or Sudan III *Stain for Fat*

These stains are used to demonstrate neutral fat in the tissue cells. For this purpose formalin fixation is advisable and frozen sections are necessary as the fat is completely disolved out in the ordinary process of paraffin embedding. Fat stains a deep red. The tissue cells may be conveniently counterstained with a diffuse haematoxylin stain.

Levaditi Stain for Spirochaetes

This is a silver impregnation method for demonstrating spirochaetes in the tissues. Here a neutral formalin fixative is necessary. It is a process which requires some days to complete, the tissue being stained in bulk. The spirochaetes stand out black against a yellow background.

Best's Carmine Stain for Glycogen

Here it is essential that the tissue be fixed in not less than 90% alcohol. The tissue is then embedded in paraffin or celloidin and the cut sections stained first in iron haematoxylin. Following this they are stained in Best's Carmine solution which stains glycogen a brilliant red.

In order to become at all proficient in the art of staining histological preparations, it requires a certain amount of experience. A method of procedure can be easily outlined but it takes a little time to acquire the necessary skill for the proper carrying out of the details. This can only be attained through actual experience.

While the success of a laboratory in a great measure is due to the character of the work done by the technical staff the final results depend upon the man who supervises the work, and finally has to pass judgment and give his opinion as to the pathological process as revealed by the histological preparations.

CERTAIN PRINCIPLES OF LIVING MATTER IN BIOLOGY AND MEDICINE

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THERE are two factors always evident in the progress of human knowledge. One of these depends solely on the practical application of ascertained facts. The other is termed theoretical. The proponents of these factors are found ridiculing and praising, obstructing and assisting one another. At times the practical method is applied first, and only the hunt for the meaning of the result brings out the theoretical explanation. This is largely true of the growth of therapeusis. The explanation came long after the established practice. But unchecked by theoretical knowledge there was always danger of excess. As, for instance, in the case of blood-letting as our fathers followed it, increase in theoretic knowledge has justified the procedure but limited its applicability. On the other hand, the whole bacteriological development has been based on accurate theoretical knowledge leading to practice and the practice, in this case, has increased so enormously in precision and scope that it may be described as a new phenomenon.

Safety in practice demands a type of conservatism that is best achieved by the sequence of theoretical to practical rather than the reverse. The aim of education is knowledge leading to reasoned and restrained action. The theories and reasons back of action are longer enduring and more universal than the action or in many cases the results of the action.

When we undertake to study life, as in biology, the two aspects crop up at once. We may study facts that lead directly to action or we may delve deeper into reactions that are common to all life manifestations. So far as medicine is concerned the relation of biology lies in an explanation of life principles rendering method safer and more firmly based. The general laws of life are applicable to other living things as well as to man. We may examine the simplest organisms and draw conclusions from them that apply to and influence, or have applied to and have influenced, the highest types. In fact the steps of gradation from the one to the other are so fine and so nearly continuous that one is tempted to consider that all life is one life.

Men have long struggled with the question of what life is and how it arose. Attention was early directed to the unicellular organisms, but the visible unicellular organism is already far advanced in differentiation and although attempts have been made to reproduce conditions that would allow the formation of living organisms from non-living matter they have either been a complete disappointment or so doubtful as to the true exclusion of living matter that they are useless. However the study of the anatomical forms of these living creatures yields evidence on the one hand by their essential simplicity and on the other by the complexity of species of the length of their existence on the earth. It is an enormous step from bits of living material with little beyond the external form visible such as bacteria to complicated forms with specialized parts. Physiological and anatomical associations are well illustrated by this differentiation. The nucleus contains the hereditary substance and exercises control over metabolism. Mouth, pharynx, gullet and anal spot are differentiated for the digestive processes. The contractile vacuole acts as an excretory organ. Pseudopodia flagella or cilia produce movement. Trichocysts develop as offensive organs. Calcareous or siliceous shells form a protection. The shells of Foraminifera and Radiolarians in countless numbers and of infinite variety settling in the sea have formed layers of bottom ooze and eventually of rock many miles in thickness.

The complication in these forms is partly an effort to overcome the disadvantages of increase in size. The volume of a sphere increases more rapidly than the surface area enclosing it. Food material and oxygen come from the surface. Projections from the surface, growth in one plane, rapid locomotion, streaming protoplasm, vacuoles or spaces within the protoplasm all tend to increase the surface more nearly in proportion to the volume. But eventually a stage is reached where these artifices will not suffice. Then the necessity for division arises. There are two major ways in which the unicellular forms accomplish this. The one is a simple splitting into two. The volume to surface ratio is thus decreased and each of the daughter cells absorbs food materials and grows. The other is a process of spore formation by which one individual may very rapidly increase by multiple division.

This is an effort to overcome the disadvantages of a fortuitous and rapidly changing environment favourable or unfavourable. Since this condition occurs most markedly under parasitic habits of life the higher unicellular parasites exhibit the most complicated spore formation. The same end is reached by another means in gemmation or bud formation where small pieces of the parasite give rise to new individuals. This method is developed largely by the plant forms. Unfavourable conditions of the environment require special protective measures and the lower one-celled forms develop resistant spores and the higher form cysts about themselves. Growth is then impossible but life is maintained until favourable conditions arise again. Rapidly changing conditions may be met also by the development of forms capable of living under these conditions. Variation in form and life habit requires differentiation at division or the addition of new chemical substance to the living material. The latter is accomplished in the unicellular forms by a type of conjugation. In its essentials this is the exchange of hereditary substance between two individuals and occurs in the unicellular forms by the division and transfer of portions of the nucleus. The reproductive stages between generations in the higher plants and animals all descend to this simple unicellular stage and as in the unicellular forms reproduction may be either by simple division, that is, non-sexual, or by the union of the hereditary materials of two individuals, sexual reproduction.

The process of cell division may result in either independent or inter-dependent organisms. The independent condition characterizes the unicellular types and yet they show certain attempts to produce an association of individuals. The simplest association is when the cells after division remain together either in a straight line or in a plane. In other forms a gelatinous matrix encloses irregularly placed cells or supports a peripheral layer of organisms. The latter type reproduces the early growth stages of the many celled forms or metazoa. There is also found in the unicellular type internal division resulting in a multinucleate condition. This is probably a degenerative result and not a stage in form development. Physiologically the unicellular organisms remain as separate units. The attachment has not acquired to any marked degree the extra bond of inter-dependence that characterizes the metazoa.

The biological world in spite of its obvious differentiation shows an essential unity. As knowledge increases the steps that lead from one type to another are continuously being reduced in size. Each class in itself is a unit but only a stage in the whole development. The characters that differentiate such large divisions as the plant and animal worlds are found associated together in the flagellate protozoa. In Euglena along with active motility is found the ability to synthesize carbohydrates. That property is due to the development of chlorophyl which is a characteristic of plant organisms. Yet this form is anatomically identical with other purely animal forms. It then combines the properties of a plant and an animal. Such intergrading steps are found to occur in any classification of living organisms that is attempted. The same resultant physiological effect is reached by the symbiotic association of plant and animal cells. The unicellular animal, Paramoecium bursaria devours the unicellular alga Chlorella vulgaris, but the

latter resists the digestive juices of the Paramoecium and lives and divides within the protoplasm of its host. Both are capable of living an independent life in this case. This is an association where the animal produces excess carbon dioxide and the plant excess carbohydrates; formed one from the other and vice-versa and mutually necessary for the living organisms. A similar symbiotic relationship is exhibited by the association of nitrifying bacteria in the root tubercles of leguminous plants. The next step in the progress is one in which, as in the case of the non-pathogenic bacteria the host without benefit to itself supports the parasite. Then the succeeding stage leads on to the development of actual harm to the host organism, and the parasite develops the characteristics that are exhibited by the pathogenic bacteria.

The biological law that governs the parasitic habit is the association of an increased reproductive capacity in a suitable medium with a restricted availability of the medium. These forms need both rapid division rates and at the same time a means of tiding over the periods when they are unable to find a medium suitable for their full growth. Spore formation and encystment are then outstanding features of successful parasites. They also produce in their life activities, substances that are detrimental not only to their host but to themselves and so either by destruction of their medium of growth or by poisoning themselves they tend to be self limiting. The latter characteristic is common to all living organisms in a greater or lesser degree but is especially prominent in the parasites. Parasitic organisms are so closely tuned to existence in special media that they exhibit localized association to the highest degree. Avian, bovine and human tubercle bacilli are forms that show this association very closely. Avian tubercle occurs in birds but not in the human. Bovine tubercle has a limited spread to the human but there tends to attack the bones of the young. Human tubercle bacilli show preferences for certain races such as the red-skinned tribes and even for certain hereditary stocks within the races. The medium and the organism must both be suitable for the occurrence of the rapid increase in numbers that is characteristic of parasitic development. There are then two methods of attack on the advances of such parasitic forms. One means is that of rendering the medium unsuitable and under this are grouped the various types of inoculations and vaccinations as well as properly balanced and sufficient rations and healthy conditions of living. All these methods render the ground unsuitable for the propagation of the parasite. The other means attacks the organisms, and the use of poisonous compounds for injection and for cleansing, the sterilizing and isolation methods—all aim at the eventual destruction of the injurious living agent either by violent death or by starvation when the food supply is removed.

In the field of protozoal parasites the associations are even closer. The various stages of the life history often do not occur in one and the same medium but require specific new media for their development. In the malarial organism while a series of rapid asexual reproductive methods occur in both the human and the mosquito the sexual reproductive phase occurs only on transference from the mammal to the insect medium. The same type of restriction of certain life stages to a second host are found in the case of sleeping sickness where the second host is the tse-tse fly. The restriction of the medium is further empha-

sized by the fact that it is one species of mosquito and one species of fly that is capable of acting as the nutrient medium in these cases. This close association renders possible greater accuracy and a more definite hope of control of parasitic types. In the simplest type of cultures there are found a series of organisms that are present in succession. In a hay infusion for example, bacteria appear, later flagellates and ciliates, and still later minute worms and small shelled forms. Each of these has its beginning, its dominant period and finally it is replaced by some other type better suited to exist in the now changed environment. This process is associated probably with the fact that organisms produce in their life activities substances that are destructive to themselves. Yet it illustrates the beginning of that law of specific reactions that is carried to such far reaching conclusions in parasites where the medium of growth is so necessary to the activities of the cell living in it that the cell apart from the medium leads only a quiescent life. The essential process occurring in cancer growth is the rapid increase of cells by mitosis. This process is permitted by the reduction in the amount of substances preventing growth or the increased capacity for growth that the cells possess. As such the process is at least analogous to the reactions of infusorial and bacterial cultures since nutrient materials, favourable conditions and living cells must be present in both cases. It is found that unfavourable conditions can coexist in infusorial cultures with both sufficient food material and cells present. No growth or increase in number is then possible. The study of these unfavourable conditions is then the central point of attack on the control of cell growth.

Even in the very limited part of biological study treated of it is possible to pick out general principles that apply universally. To reduce the material to the simplest elements possible is a valuable method of gaining a perspective. The wider field of general biology leads by fine and still finer gradations to the relationship of man and his environment. The general principles that control living organisms give basis and background to the physical and mental studies that make up the practical field of medicine.

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*ON SOME PRINCIPLES IN THE EMPLOYMENT OF VACCINES

H. B. MAITLAND

The Bactericidal Power of Serum

IN the first part of this paper it has been stated that normal serum is not bactericidal for *staphylococcus* or *streptococcus*, but that after a proper stimulus, the leucocytes may excrete bactericidal substances, which can be detected by measuring the bactericidal value of the serum. The reaction has been considered in connection with the function of leucocytes..

On the other hand there are numerous organisms for which normal serum is decidedly bactericidal. As an example one may take *B. typhosus*. If *B. typhosus* is added to normal serum, only a small proportion of the organisms survive. The remainder are destroyed as a result of the anti-tryptic power of the serum and in part also by bacteriolysins. That the anti-tryptic power of the serum is a destructive agent can be shown by making a similar inoculation into serum whose anti-tryptic power has been neutralized with an appropriate quantity of trypsin. It will then be found that the serum possesses little bactericidal action, in fact it becomes a very good medium. Bacteriolysin for *B. typhosus* is not present in any considerable amount in normal serum but in immune serum it plays an important part in destruction.

B. typhosus has been chosen as an example because inoculation against typhoid fever has become so firmly established as a means of preventing the disease. In the experiments which led to its adoption as a recognized practice the bactericidal power of the serum was employed as an index to follow immunity changes. After inoculation the bactericidal power of the serum increased. There was a temporary early depression—a negative phase—followed by a rise. The curve was similar to that described for the opsonic index, and it was rightly argued that such a rise indicated increased immunity.

The duration of immunity after anti-typhoid inoculation is naturally of much interest. Increase in bactericidal power may persist for six months or more. The same may also be said for the agglutination titre. The question is whether or not they indicate the actual duration of immunity to typhoid. Experience has shown that reinoculation should be practised at least every two years, if immunity is to be ensured. Where the chances of exposure are great, annual inoculation is advisable. That is the practical result of experience. The theoretical consideration of the relation of increased bactericidal power and agglutinin titre to the duration of immunity is however the point under discussion. As long as they are maintained at a level higher than normal one may suppose that the body is still reacting to the stimulus of inoculation and that immunity is being maintained. When they begin to decrease, one surmises that the protection diminishes. Immunity is however not entirely referable to antibodies. Agglutinins in themselves are not highly protective, bactericidal substances are more so but in addition

*(*Continued from last issue*)

to antibodies one must consider the ability of the tissue cells to react. During the phase of increased antibody content in the blood there is, in addition to the protective influence of the antibodies themselves, the factor of maintained cellular activity. Decrease in antibodies is an indication that cellular activity is lowered. But even after the antibody level has returned to normal the cells remain impressed with the reaction they have undergone. They retain an ability to react more quickly and more vigorously to a new stimulus. That is to say if an occasion should arise where an individual becomes exposed to infection, the entrance of *B. typhosus* would incite a more vigorous reaction than in an uninoculated person and the vigour and promptness of the reaction might make the difference between infection and resistance. Protection after inoculation in any case is a relative matter. It must always be thought of in relation to dosage. When one says that a person is protected from typhoid fever or that protection lasts for a certain time after inoculation he really means that the usual dosage of typhoid bacilli to which people are ordinarily exposed would not be sufficient, in his case, to incite the disease. A much larger dose would be required and even if the individual succumbed to it the probability is that the disease would run a milder course than usual. The time at which protection ends is thus also relative. After antibodies have disappeared from the blood the quality for vigorous reaction retained by the cells affords some degree of protection. Typhoid fever contracted by an individual inoculated two years or more previously is likely to run a milder course than in some one who has never been inoculated.

Although this discussion has been concerned with typhoid fever the principles of protection in relation to dosage and the relation of antibodies and reacting quality of cells to the level of immunity are not confined to this one example. They are capable of wide application to all forms of protective inoculation.

We are purposely omitting a discussion of protection against diphtheria obtained by the injection of toxin-antitoxin mixtures. A consideration of the subject in detail would carry the paper beyond its required length. Suffice it to say that the principles discussed in this section apply. The immunity is in part due to the development of antitoxin by the patient, following inoculation, and in part no doubt depends upon an ability of the cells to react more efficiently when a possibility of infection arises.

Skin Reactions

The significance of skin reactions in immunological studies will be more readily comprehended if, for purposes of discussion, they are considered in two groups and if a clear differentiation of the principles underlying each type of reaction is sought for. As an example of the first group—chosen in order to continue the discussion of typhoid fever—one may take the typhoidin reaction. Along with it should be placed the tuberculin reaction and the mallein reaction. All these reactions are induced by injecting into the skin an extract of the bacteria concerned, in such quantity that a normal person will not react. Individuals whose cells have become hypersensitive through infection or inoculation will respond to the injection by developing a local reaction which consists of swelling, erythema, etc.

The typhoidin test has been applied to the study of immunity in typhoid fever. Individuals who have recovered from typhoid or who have recently had antityphoid inoculation show a "positive test". In other words the cells of the skin react more vigorously than normal when an extract of *B. typhosus* is injected intradermally. The test is based therefore upon the reacting quality of the cells and the relation it has to the duration of immunity after antityphoid inoculation will readily be understood in view of the discussion set out in the last section. Gay has used it to indicate the time when reinoculation becomes necessary. If an individual gives a "positive" reaction his immunity may be considered satisfactory. (This statement needs qualifying for which the reader is referred to Gay's monograph). A "negative" reaction discloses need for further immunization.

The tuberculin test and the mallein test, particularly the former, have found a place in diagnostic methods, but they do not enter the scope of this paper.

The second type of skin reaction may be illustrated by the Schick test. The technique calls for the injection of a stated quantity of diphtheria toxin. The development of a reaction relates to the antitoxin content of the blood. If there is sufficient antitoxin in the blood to neutralize the injected toxin no reaction will occur. The irritating effect of the toxin will have been inhibited. If however the blood is weak in antitoxin, the injected toxin will not be neutralized and a reaction will develop. The Schick test is therefore a criterion of the antitoxin content of the blood and, since immunity or susceptibility to diphtheria is determined for the most part by the amount of circulating antitoxin, the reaction is also a criterion of the state of immunity to diphtheria. It has been employed to detect those who are susceptible, to determine the onset of immunity following toxin-antitoxin inoculation, and to indicate its duration.

General Considerations

The foregoing review of methods used to appraise the result of inoculation has aimed at a discussion of some of the principles upon which the practice of inoculation is based. Further important principles may be considered along with some points of general interest.

Vaccines and local immunity. It is well known that the tissues or organs of the body are not equally susceptible to infection. Accidental wounds of the skin tend to heal without serious infection. The throat after tonsillectomy heals well in spite of the presence of many bacteria. Infection in the Pouch of Douglas is apt to be less serious than a similar infection of the upper abdomen. An ischio-rectal abscess after incision is connected with the bowel but heals regularly. Localities that are frequently exposed to bacteria tend to resist infection. It is not a question of circulating antibodies but of fixed tissue cells. Experimental evidence goes to show that this local immunity may be increased (at any rate, in certain important instances) by the application of vaccines, and it is only necessary to recall that many organisms have a limited portal of entry, to realize the possible importance of applying this measure in prophylaxis.

Intratracheal administration of a saline pneumococcus vaccine to monkeys has had a protective influence. The vaccinated monkeys

resisted subsequent intratracheal inoculations of living pneumococci that proved fatal to non-protected animals. The protection was not associated with antibodies. It appeared to be a result of local immunity in the tissues of the trachea and bronchi.

Working with anthrax it was found possible to immunize the skin locally, and with streptococci local immunity has been developed in the pleural cavity.

In typhoid fever the immunity of the intestinal wall has received attention. Rabbits have been given saline vaccine by mouth, preceeded by ox bile which in some unknown manner renders the intestine amenable to the action of typhoid vaccine. After vaccination the rabbits have resisted inoculations of *B. typhosus* in doses fatal to normal rabbits. Again no antibodies were concerned. The immunity was considered to be an increased resistance of the intestinal wall to the invasion of *B. typhosus*.

It is evident that vaccines can influence local immunity. The problem is to know to what extent local immunity is responsible for the protection conferred by one attack of a disease, as after small-pox, syphilis, typhoid fever, typhus fever, scarlet fever, etc. One also wonders to what extent it is important in the protection afforded by vaccination against, for example, small pox, typhoid fever or diphtheria. A more practical problem is the application of deliberate local vaccination to man. There would be no technical difficulty in giving vaccine as an intratracheal spray to prevent pneumonia, but as the method has not been tried sufficiently one cannot pronounce upon its practical value. The oral administration of typhoid vaccine has been tested. An epidemic in a village in the north of France, and an outbreak in some schools in Paris have afforded opportunities. The reports are favourable. There is no unpleasant reaction to vaccine administered in this way and since antibodies are not involved it is claimed that the negative phase is eliminated.

The most recent pronouncement upon oral administration of vaccine comes from Calmette at the Pasteur Institute in Paris. His word is one of caution. His opinion is that the method is still more or less experimental and that too much reliance should not be placed upon it as a means of inducing protection. At any rate we should not leave the certainty of subcutaneous vaccination against typhoid fever for the easier, but at present more doubtful method of oral vaccination. Here the subject remains at present. The future may give it greater importance.

Non-specific protection afforded by vaccines. Pasteur's original conception was that protection afforded by inoculation was specific, but by degrees it has been realized that prophylactic vaccination induces protection, at least some degree of protection, against bacteria other than those closely related to the organisms contained in the vaccine. One example will suffice. To quote from Sir Almroth Wright, "I confess to having shared the view that immunization is always strictly specific. Twenty years ago, when it was alleged, before the Indian Plague Commission, that anti-plague inoculation had cured eczema, gonorrhoea and other miscellaneous infections, I thought the matter undeserving of examination. I took the same view when it was reported in connec-

tion with anti-typhoid inoculation that it rendered the patients much less susceptible to malaria. Again, seven years ago, when applying pneumococcus inoculations as a preventive against pneumonia in the Transvaal mines, I nourished exactly the same prejudices. But here statistical results which were obtained in the Premier Mine demonstrated that pneumococcus inoculations had, in addition to bringing down the mortality from pneumonia by 85 per cent., reduced also the mortality from 'other diseases' by 50 per cent. From that on we had to take up into our categories the fact that inoculation produces in addition to 'direct' also 'collateral' immunization."

The employment of vaccines in non-specific therapy. The non-specific protective value of vaccines has been referred to in the last section. Their non-specific therapeutic uses will be considered here. Vaccines have been employed as non-specific remedial agents in common with a great variety of materials such as horse serum, peptone, casein, milk, defibrinated autogenous serum, colloidal preparations of metals, etc., etc. Such non-specific remedies have been advocated and have found a place in the treatment of numerous diseases. They are not protective measures; and the use of vaccines as non-specific agents should be carefully distinguished from vaccines used specifically for treatment or prophylaxis.

In non-specific therapy the common practice is to administer intravenously. Thus, for example, intravenous injection of vaccine has been given in acute arthritis, septicaemia, typhoid fever, to mention only three. Beneficial results are sometimes obtained. A full discussion of the subject may be found in a monograph by Petersen. In this place it is only desired to point out that all forms of non-specific therapy are empirical. The reaction following the injection is not well understood; and we should like to point out that many of the extravagant claims found in advertising literature accompanying commercial preparations are based on exceptional cases. One hears an occasional report from a reputable physician, or student, of a striking result following the administration of some preparation or another. We would do well to ask in each instance whether the result is based on any recognized principle, or whether it is an effect of non-specific therapy, in which some other agent might very well have been substituted for the one employed. Zinsser remarks in this connection, "finally we would like to state that while including this problem of non-specific therapy in this book because of its obvious bearing on general problems of resistance, we do not think that the treatment, at the present time, has reached the stage at which it can be considered as anything but experimental, and should not be attempted by physicians who have not very thoroughly familiarized themselves with clinical records, and who do not approach it very distinctly with the precautionary accuracy of a worker conscious that he is carrying out an experimental measure."

The most satisfactorily consistent results will come to those who follow most faithfully the principles of inoculation as far as they are known.

Indications for the therapeutic use of vaccines. After an infection has become established the only aim that vaccine therapy can have is to augment the forces that are working toward the eradication of the

micro-organisms. The questions that must be asked in each individual case are (1) What are the forces operating against this infection? (2) Can they be augmented by the injection of vaccine, in other words, can the body be stimulated to react more efficiently than it is reacting? (3) If more antibodies should be produced or the leucocytes made more efficient, will the nature of the lesion permit these destructive agents to reach the bacteria?

With regard to the first question, each type of infection must be considered by itself. In general it can be stated that vaccines have found their greatest success in infections due to pyogenic bacteria, particularly *staphylococcus*, *streptococcus*, *gonococcus*, *B. coli* and related organisms, and *B. influenzæ*.

The problem of the second question can only be decided by considering each case on its merits. In acute infections such as pneumonia, streptococcus cellulitis, meningitis, endocarditis, septicaemia, typhoid fever, where there is general infection or general bacterial intoxication, shown by fever or other signs, one cannot hope to accomplish much by introducing vaccine. It is true that Wright has recently shown that in acute infections the leucocytes may be stimulated by carefully regulated doses of vaccine and the principle holds out promise that something may be accomplished. As yet the matter is hardly out of the experimental stage, but one may look for developments along this line. The well known field for vaccine therapy is the localized subacute infection where the organisms are prevented from extensive invasion but where the defensive reaction is not sufficient to completely overcome them. Furunculosis, acne, sycosis, bronchitis, infections of the nasal sinuses, pyelitis, cystitis, urethritis, prostatitis are typical. When the infection is localized, when signs of general bacterial poisoning are slight or intermittent, the conditions that indicate vaccine therapy exist and it is in just such conditions that the best results are consistently obtained.

The third question merits a separate section.

Aids to therapeutic inoculation. It will avail little to increase the resisting forces of the body if they cannot be transported to the area occupied by the microbes. As an aid to inoculation one must often have recourse to surgical measures.

It should be remembered that leucocytes do not swim. They crawl. They cannot transport themselves through fluid. Bacteria in a collection of fluid in the pleural cavity, for example, are free from phagocytosis. Phagocytosis will be accomplished only on surfaces, and this fact affords one justification for draining or removing collections of fluid or pus.

Another aid to inoculation is a free flow of tissue fluids into a wound or an infected surface. Fresh tissue fluids are bactericidal and bring antibodies. In contrast, fluids that stagnate in pockets of infection soon become a good culture medium. The disintegration of leucocytes liberates trypsin which soon neutralizes the natural and tryptic power of the tissue fluids, and in doing so convert them from a defensive force into a favourable medium for bacterial growth. Efficient drainage will do much to prevent stagnation. In some cases the application of hypertonic saline to open wounds has been markedly beneficial. Particularly was this true of war wounds.

Drainage of an infected area not only provides it with a better supply of antibodies; in addition it removes, or allows to escape, the harmful products of infection. When they are pent up they are absorbed and produce general effects. Leucocytes especially are sensitive to the damaging influence of these products, and the mere opening of an abscess is regularly followed by improvement in phagocytic function.

The type of vaccine and the question of dosage. For routine purposes the efficacy of saline vaccines has been proved. Sensitized vaccine is said to give less unpleasant reaction but has not generally found favour. Detoxicated vaccines, made on the principle of retaining the antigenic fraction of bacteria and discarding the non-antigenic irritating fraction, have had a temporary prominence. Lipoid vaccines made by impregnating dried bacteria with oil in order that they might be absorbed more slowly by the tissues have been shown to be inferior to saline vaccines. Commercial preparations of bacterial extracts of various sorts are rather extensively used by physicians because they are well advertised and systematically sold. One suspects that they are more profitable to the manufacturer than saline vaccines. The pseudo-scientific advertising propaganda of some commercial houses does much to obscure the more reliable, if somewhat less extravageant, views by which the practice of inoculation should be regulated.

The relative merits of vaccine made from a stock culture and one made from a culture of the patients own organism is a point that frequently arises. There is little to be said apart from opinion. By preference one uses an autogenous vaccine but stock vaccines frequently do as much good. The elaborate formulae of mixed stock vaccines advertised by various firms, where one is given a choice of twenty or more varieties, each with its own peculiar virtue, is the outcome of commercial instincts rather than the development of scientific principles. Best results will be ensured by giving the patient a vaccine containing the organisms with which he is infected, and this can only be determined by bacteriological examination.

Regarding dosage, only the most general hints can be suggested. Again opinion decides. Most physicians aim to start with a small dose that will not cause a local reaction and to increase the amount gradually. A mild transient local reaction is not objected to, but a severe local reaction or a general reaction indicates too large a dose. Injections are usually given at intervals of from four to six days.

For prophylaxis, the dose is usually specified and is larger than for treatment. It is not necessary to avoid a general reaction or to fear a negative phase, because infection is not present. Gay believes that in antityphoid vaccination it is the quantity of vaccine that matters, and the subdivision of the total quantity into two or three doses and the spacing of the inoculations are of little importance.

It is hoped that these brief outlines of some of the principles underlying the practise of inoculation will lead those who may read them to a more thoughtful and intelligent point of view in the employment of vaccines. There is still much of empiricism connected with vaccine therapy and problems exist upon which only opinion can be expressed. We do not intend to discourage empiricism .Consistently successful empiricism is justifiable practise. But let us separate empiricism from

principles established upon an experimental foundation. It is only by having clearly in mind which we are following that the best results from the administration of vaccines can be obtained.

The following references will assist those who would like a fuller discussion of some of the points referred to in this article.

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Wright and Colebrook,—Technique of the Test and Capillary Glass Tube, 2nd Ed. Constable, 1921.
Wright, Colebrook and Storer,—New Principles in Therapeutic Inoculation, Lancet, Feb. 24th, March 3rd and 10th, 1924.
Colebrook and Storer,—On Immuno-transfusion, Lancet, 1923, Vol. 2, p. 1,341.
Kohner—Infection, Immunity and Biologic Therapy, 3rd Ed. Saunders, 1923.

Medical Sick Benefit Fund

Any undergraduate who is entitled to benefits from the Medical Sick Fund is requested to send his application at once to R. J. Heffring, Assist. Sec.-Treas., Med. Society, Room 107, Anatomy Building.

The Medical Society appreciate very much the action of the graduating year in presenting the MEDICAL JOURNAL with $120.00 to aid in extending and carrying on the publication.

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NOTES AND COMMENTS

The final open meeting of the Medical Society was held in the Anatomy Lecture Room on Tesday, March 18th. Dr. Austin F.R.C.S. of Queen's University gave a very interesting and instructive address on the History of Syphilis. Dr. Austin has done considerable original work on this disease while stationed at the Middlesex Hospital, London, Eng. He pointed out that though a great deal of evidence went to show that Columbus and his party carried the disease to Europe in 1492 the question was by no means settled. The solution, if forthcoming, doubtless lay in the examination of the bones in various American cemeteries. Prof. O. Klotz, hon-treas. of the society acted as chairman, and Prof. Henderson and Dr. Ryerson presented the various athletic trophies won during the year. Mr. James Sinnott of the graduating year and Mr. Peacock of 2T7 rendered vocal and violin solos respectively. These were greatly appreciated and heartily encored.

The Year in Athletics

The Meds. have had a very successful year in Athletics. We have had a very large number of men playing on the University teams. We won three interfaculty cups. F. J. Scott, 2T4, won the tennis; Sr. Meds, hockey and Jr. Meds., basket ball. Meds have stood very high in other lines of sport.

The following men have been granted their Medical Colors:

2T4: F. J. Scott—Tennis; H. K. Hilliar—Rugby; H. R. Buckley—Basket Ball and Indoor Base Ball; R. W. Boyden—Hockey; W. D. Hawkins—Indoor Base Ball; C. N. O'Neill—Indoor Base Ball; S. J. Scott—Indoor Base Ball;

2T5: T. G. McCartney—Soccer; S. R. Beatty—Soccer.

2T6: A. W. Ham—Tennis; F. J. Bull—Swimming; W. D. Higgs—Swimming; H. K. Moir—Swimming; W. H. Hatfield—Swimming; J. M. Miller—Track; A. F. Thayler—Wrestling, J. F. Dryer—Soccer and B. Rugby; M. I. Sparks—Lacrosse; H. M. Ross—Lacrosse.

2T7: T. E. Flommerfelt—Swimming; L. A. Clark—Track; L. B. Bier—Rugby; R. C. Grant—Rugby; F. B. Hamilton—Rugby; K. C. McGibbon—Rugby; E. V. Shute—Boxing; J. W. R. Webster—Wrestling; R. A. White—Hockey; H. D. Marritt—Hockey and Rugby.

2T8: H. E. Rykert—Rugby; H. F. Robertson—Boxing, A. O. Killpatrick—Lacrosse; L. M. Mullen—Rugby.

The colors are still to be awarded for basket ball. There are several freshmen on the championship team who will receive the M with their year numeral when they pass their examinations.

The "athletic stick" which is given annually to the man in the graduating year who has taken the most outstanding part in athletics while in the faculty was presented to "Goldie" Gray by Prof. Hendry at the Graduation Banquet.